

## EAST Search History

Ref #	Hits	Search Query	DBs	Default Operator	Plurals	Time Stamp
L1	416	(alpha chains) and trimer	US-PGPUB; USPAT; DERWENT	ADJ	ON	2007/07/24 11:04
L2	417	(alpha chain\$) and trimer	US-PGPUB; USPAT; DERWENT	ADJ	ON	2007/07/24 11:05
L3	3	(alpha chain\$).ab. and trimer	US-PGPUB; USPAT; DERWENT	ADJ	ON	2007/07/24 11:11
L4	2	(alpha chain\$)and trimer.ab.	US-PGPUB; USPAT; DERWENT	ADJ	ON	2007/07/24 11:07
L5	3	(alpha chain\$)and trimer\$.ab.	US-PGPUB; USPAT; DERWENT	ADJ	ON	2007/07/24 11:07

10554068

File 5: Biosis Previews(R) 1926-2007/Jul W3  
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Set	Items	Description
S1	112	(ALPHA())CHAIN) AND LAMININ
S2	9	((ALPHA())CHAIN) AND TRIMER?) AND LAMININ
S3	0	CHIMER? AND TRIMER? AND COLLAGEN AND LAMININ
S4	0	CHIMER? AND (TRIPLE()HELI?) AND LAMININ
S5	0	CHIMER? AND (TRIPLE()HELICAL) AND LAMININ
S6	7203	LAMININ AND COLLAGEN
S7	29	S6 AND CHIMER?
S8	3	(ALPHA())CHAIN) AND CHIMER? AND LAMININ
S9	89	(PRO()ALPHA()CHAIN?)
S10	0	S9 AND CHIMER
S11	0	S9 AND CHIMER?
S12	1	S9 AND S6
S13	13	(FUSION()PROTEIN) AND S6

? t s2/7/1-9

2/7/1

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0019727659 BIOSIS NO.: 200700387400

The requirement of the glutamic acid residue at the third position from the  
carboxyl termini of the %laminin% gamma chains in integrin binding by  
laminins

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JOURNAL: Journal of Biological Chemistry 282 (15): p11144-11154 APR 13  
2007 2007

ITEM IDENTIFIER: doi:10.1074/jbc.M609402200

ISSN: 0021-9258

DOCUMENT TYPE: Article

RECORD TYPE: Abstract

LANGUAGE: English

ABSTRACT: Laminins are the major cell-adhesive proteins in the basement  
membrane, consisting of three subunits termed alpha, beta, and gamma. The  
putative binding site for integrins has been mapped to the G domain of  
the %alpha% %chain%, although %trimerization% with beta and  
gamma chains is necessary for the G domain to exert its integrin binding  
activity. The mechanism underlying the requirement of beta and gamma  
chains in integrin binding by laminins remains poorly understood. Here,  
we show that the C-terminal region of the gamma chain is involved in  
modulation of the integrin binding activity of laminins. We found that  
deletion of the C-terminal three but not two amino acids within the gamma  
1 chain completely abrogated the integrin binding activity of  
%laminin%-511. Furthermore, substitution of Gln for Glu-1607, the  
amino acid residue at the third position from the C terminus of the gamma

1 chain, also abolished the integrin binding activity, underscoring the role of Glu-1607 in integrin binding by the `%%laminin%%`. We also found that the conserved Glu residue of the gamma 2 chain is necessary for integrin binding by `%%laminin%%-332`, suggesting that the same mechanism operates in the modulation of the integrin binding activity of laminins containing either gamma 1 or gamma 2 chains. However, the peptide segment modeled after the C-terminal region of gamma 1 chain was incapable of either binding to integrin or inhibiting integrin binding by `%%laminin%%-511`, making it unlikely that the Glu residue is directly recognized by integrin. These results, together, indicate a novel mechanism operating in ligand recognition by `%%laminin%%` binding integrins.

2/7/2

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18561197 BIOSIS NO.: 200510255697

A simplified `%%laminin%%` nomenclature

AUTHOR: Aumailley Monique; Bruckner-Tuderman Leena; Carter William G; Deutzmann Rainer; Edgar David; Ekblom Peter (Reprint); Engell Juergen; Engvall Eva; Hohenester Erhard; Jones Jonathan C R; Kleinman Hynda K; Marinkovich M Peter; Martin George R; Mayer Ulrike; Meneguzzi Guerrino; Miner Jeffrey H; Miyazaki Kaoru; Patarroyo Manuel; Paulsson Mats; Quaranta Vito; Sanes Joshua R; Sasaki Takako; Sekiguchi Kiyotoshi; Sorokin Lydia M; Talts Jan F; Tryggvason Karl; Uitto Jouni; Virtanen Ismo; von der Mark Klaus; Wewer Ulla M; Yamada Yoshihiko; Yurchenco Peter D

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JOURNAL: Matrix Biology 24 (5): p326-332 AUG 2005 2005

ISSN: 0945-053X

DOCUMENT TYPE: Article; Literature Review

RECORD TYPE: Abstract

LANGUAGE: English

ABSTRACT: A simplification of the `%%laminin%%` nomenclature is presented. Laminins are multidomain heterotrimers composed of alpha, beta and gamma chains. Previously, `%%laminin%%` `%%trimers%%` were numbered with Arabic numerals in the order discovered, that is laminins-1 to -5. We introduce a new identification system for a `%%trimer%%` using three Arabic numerals, based on the alpha, beta and gamma chain numbers. For example, the `%%laminin%%` with the chain composition alpha 5 beta 1 gamma 1 is termed `%%laminin%%-511`, and not `%%laminin%%-10`. The current practice is also to mix two overlapping domain and module nomenclatures. Instead of the older Roman numeral nomenclature and mixed nomenclature, all modules are now called domains. Some domains are renamed or renumbered. `%%Laminin%%` epidermal growth factor-like (LE) domains are renumbered starting at the N-termini, to be consistent with general protein nomenclature. Domain IVb of alpha chains is named `%%laminin%% 4a (L4a)`, domain IVa of alpha chains is named L4b, domain IV of gamma chains is named L4, and domain IV of beta chains is named `%%laminin%% four (LF)`. The two coiled-coil domains I and II are now considered one `%%laminin%%` coiled-coil domain (LCC). The interruption in the coiled-coil of 13 chains is named `%%laminin%% beta-knob (L beta) domain`. The chain origin of a domain is specified by the chain nomenclature, such as alpha IL4a. The abbreviation LM is suggested for `%%laminin%%`. Otherwise, the

nomenclature remains unaltered. (C) 2005 Elsevier B.V./International Society of Matrix Biology. All rights reserved.

2/7/3

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17371967 BIOSIS NO.: 200300330263

Expression and biological role of  $\alpha$ -laminin-1.

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JOURNAL: Matrix Biology 22 (1): p35-47 March 2003 2003

MEDIUM: print

ISSN: 0945-053X (ISSN print)

DOCUMENT TYPE: Article; Literature Review

RECORD TYPE: Abstract

LANGUAGE: English

ABSTRACT: Of the approximately 15  $\alpha$ -laminin trimers described in mammals,  $\alpha$ -laminin-1 expression seems to be largely limited to epithelial basement membranes. It appears early during epithelial morphogenesis in most tissues of the embryo, and remains present as a major epithelial  $\alpha$ -laminin in some adult tissues. Previous organ culture studies with embryonic tissues have suggested that  $\alpha$ -laminin-1 is important for epithelial development. Recent data using genetically manipulated embryonic stem (ES) cells grown as embryoid bodies provide strong support for the view of a specific role of  $\alpha$ -laminin-1 in epithelial morphogenesis. One common consequence of genetic ablation of FGF signaling,  $\beta$ 1-integrin or  $\alpha$ -laminin  $\gamma$  chain expression in ES cells is the absence of  $\alpha$ -laminin-1, which correlates with failure of BM assembly and epiblast differentiation. Partial but distinct rescue of epiblast differentiation has been achieved in all three mutants by exogenously added  $\alpha$ -laminin-1.  $\alpha$ -Laminin-1 contains several biologically active modules, but several are found in  $\beta$ 1 or  $\gamma$  chain shared by at least 11 laminins. However, the carboxytermini of the  $\alpha$  chains contain five  $\alpha$ -laminin globular (LG) modules, distinct for each  $\alpha$ -chain. There is increasing evidence for a particular role of  $\alpha$ 1LG4 binding to its receptors for epithelial tubulogenesis. The biological roles of this and other domains of  $\alpha$ -laminin-1 are currently being explored by genetic means. The pathways controlling  $\alpha$ -laminin-1 synthesis have remained largely unknown, but recent advances raise the possibility that  $\alpha$ -laminin-1 and collagen IV synthesis can be regulated by pro-survival kinases of the protein kinase B/Akt family.

2/7/4

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16407503 BIOSIS NO.: 200200001014

$\alpha$ -,  $\beta$ - or  $\gamma$ -chain-specific RNA interference of  $\alpha$ -laminin assembly in Drosophila Kc167 cells

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(Reprint)

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JOURNAL: Biochemical Journal 360 (1): p167-172 15 November, 2001 2001  
MEDIUM: print  
ISSN: 0264-6021  
DOCUMENT TYPE: Article  
RECORD TYPE: Abstract  
LANGUAGE: English

ABSTRACT: Drosophila **laminin** **alphabeta** **gamma** **trimer** assembly in Kc167 cells was perturbed by chain-specific RNA interference (RNAi). The intracellular pool of alpha and gamma chains remained unchanged under beta-chain RNAi by lipofection of double-stranded RNA encoding a beta-chain partial sequence. This was also the case for the intracellular pool of alpha and beta chains under gamma-chain-specific RNAi. Nonetheless, the intracellular pool of beta and gamma chains increased markedly under **alpha**-**chain**-specific RNAi. Non-reducing SDS/PAGE revealed that some of the increased beta and gamma chains migrated as disulphide-linked betagamma dimers but that the rest migrated as monomers. Since the monomeric beta and gamma bands detected under **alpha**-**chain** RNAi were denser than the beta band under gamma-chain RNAi and the gamma band under beta-chain RNAi, respectively, beta and gamma also appeared to accumulate by forming betagamma dimers without the disulphide linkage. We suggest that interconversion of these betagamma dimers is crucial for the replaceable and selective assembly of the **alpha** **chain** for alphabeta gamma **trimer** formation.

2/7/5

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16031822 BIOSIS NO.: 200100203661

Three heterotrimeric laminins produced by human keratinocytes

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JOURNAL: Cytotechnology 33 (1-3): p167-174 July, 2000 2000

MEDIUM: print

ISSN: 0920-9069

DOCUMENT TYPE: Article

RECORD TYPE: Abstract

LANGUAGE: English

ABSTRACT: Laminins are a family of glycoproteins composed of alpha, beta and gamma chains. Five alpha (alpha1-alpha5), three beta (beta1-beta3) and two gamma (gamma1 and gamma2) chains have been cloned from human and their replaceable assembly into heterotrimers produces the variety of laminins. Reverse transcription-polymerase chain reaction of mRNAs showed that human keratinocytes express the alpha3, alpha5, beta1, beta3, gamma1 and gamma2 genes at high level among the ten cloned **laminin** chains. Western blot and immunoprecipitation of the cell lysate with antiserum directed against mouse **laminin**-1 (alpha1beta1gamma1) detected two **trimers** with the composition of alphaXbeta1gamma1 (probably **laminin**-10) with the composition of alpha5beta1gamma1 and

alphabeta1. Meanwhile, antiserum directed against a synthetic peptide of human alpha3 detected only alpha3beta3gamma2 %%%trimer%%% ( %%%laminin%%%-5). We thus show that keratinocytes produce three heterotrimeric laminins. We could not detect the assembly of alpha3 with beta1 and gamma1 chains to form alpha3beta1gamma1 ( %%%laminin%%%-6) in keratinocytes.

2/7/6

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14635979 BIOSIS NO.: 199800430226

Rat mesangial cells express two unique isoforms of %%%laminin%%% which modulate mesangial cell phenotype

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JOURNAL: Matrix Biology 17 (2): p117-130 June, 1998 1998

MEDIUM: print

ISSN: 0945-053X

DOCUMENT TYPE: Article

RECORD TYPE: Abstract

LANGUAGE: English

ABSTRACT: Rat mesangial cells express two unique isoforms of %%%laminin%%% which can be modulated by culture medium composition. To define further the nature of %%%laminin%%% expressed by cultured rat mesangial cells, synthesis of individual %%%laminin%%% chains, as well as their %%%trimeric%%% association, was examined. Based on data from Northern analysis of mRNA expression, immunoblots, immunofluorescence staining and radioimmunoprecipitation of biosynthetically labeled proteins, mesangial cells express %%%laminin%%% beta1, beta2, and gamma1 chains. Mesangial cells do not express %%%laminin%%% alpha1 or alpha2. MC produce a unique %%%alpha%%% %%%chain%%%, designated alpha'm. These %%%laminin%%% chains assemble into two major isoforms. One contains alpha'mbeta1gamma1, co-precipitates with entactin and is assembled into the fibrillar extracellular matrix. The second isoform contains alpha'mbeta2 and a presumed gamma chain that migrates in gel slightly ahead of gamma1. The beta2-containing isoform is concentrated in punctate sites on the cell surface. In addition, mesangial cells display different phenotypes when plated on %%%laminin%%%-1 (alpha1beta1gamma1), as compared to purified beta2. An LRE-containing peptide of %%%laminin%%% beta2 serves as an attachment site for mesangial cells and is sufficient to induce the phenotype observed with intact beta2. These data suggest that %%%laminin%%% isoform expression plays an important role in mesangial cell phenotype and function.

2/7/7

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14147562 BIOSIS NO.: 199799781622

The %%%alpha%%% %%%chain%%% of %%%laminin%%%-1 is independently secreted and drives secretion of its beta- and gamma-chain partners

AUTHOR: Yurchenco Peter D (Reprint); Quan Yong; Colognato Holly; Mathus  
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JOURNAL: Proceedings of the National Academy of Sciences of the United  
States of America 94 (19): p10189-10194 1997 1997  
ISSN: 0027-8424  
DOCUMENT TYPE: Article  
RECORD TYPE: Abstract  
LANGUAGE: English

ABSTRACT: A mammalian recombinant strategy was established to dissect rules of basement membrane laminin assembly and secretion. The alpha-, beta-, and gamma-chain subunits of laminin-1 were expressed in all combinations, transiently and/or stably, in a near-null background. In the absence of its normal partners, the alpha chain was secreted as intact protein and protein that had been cleaved in the coiled-coil domain. In contrast, the beta and gamma chains, expressed separately or together, remained intracellular with formation of beta-beta or beta-gamma, but not gamma-gamma, disulfide-linked dimers. Secretion of the beta and gamma chains required simultaneous expression of all three chains and their assembly into alpha-beta-gamma heterotrimers. Epitope-tagged recombinant alpha subunit and recombinant laminin were affinity-purified from the conditioned medium of alpha-gamma and alpha-beta-gamma clones. Rotary-shadow electron microscopy revealed that the free alpha subunit is a linear structure containing N-terminal and included globules with a foreshortened long arm, while the trimeric species has the typical four-arm morphology of native laminin. We conclude that the alpha chain can be delivered to the extracellular environment as a single subunit, whereas the beta and gamma chains cannot, and that the alpha chain drives the secretion of the trimeric molecule. Such an alpha-chain-dependent mechanism could allow for the regulation of laminin export into a nascent basement membrane, and might serve an important role in controlling basement membrane formation.

2/7/8

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14050908 BIOSIS NO.: 199799684968  
Disulfide-bonding between Drosophila laminin beta and gamma chains is essential for alpha chain to form alpha-beta-gamma trimer  
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JOURNAL: FEBS Letters 412 (1): p211-216 1997 1997  
ISSN: 0014-5793  
DOCUMENT TYPE: Article  
RECORD TYPE: Abstract  
LANGUAGE: English

ABSTRACT: Assembly of Drosophila laminin alpha, beta and gamma chains was analyzed by immunoprecipitation of the lysate from metabolically

radiolabeled Kc 167 cells with chain-specific antibodies followed by two dimensional electrophoresis in which nonreducing and reducing SDS gel electrophoresis are combined. Precipitation of monomeric beta (or gamma) with anti-gamma (or -beta) antibody revealed that beta and gamma form stable dimer before they are disulfide bonded to each other. In contrast, alpha associates with neither monomeric beta, monomeric gamma nor beta-gamma dimer without disulfide-bonding but only with disulfide-bonded beta-gamma dimer to form alpha-beta-gamma %%%trimers%%%. These results thus demonstrated that the interchain disulfide-bonding between beta and gamma is essential for alpha to form alpha-beta-gamma %%%trimer%%%. We also found that the alpha-beta-gamma %%%trimer%%% can be secreted with a chain either disulfide-bonded or not bonded to the disulfide-bonded beta-gamma dimer.

2/7/9

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13931163 BIOSIS NO.: 199799565223

The %%%laminin%%% alpha chains: Expression, developmental transitions and chromosomal locations of alpha-1-5, identification of heterotrimeric laminins 8-11, and cloning of a novel alpha-3 isoform

AUTHOR: Miner Jeffrey H; Patton Bruce L; Lentz Stephen I; Gilbert Debra J; Snider William D; Jenkins Nancy A; Copeland Neal G; Sanes Joshua R  
(Reprint)

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JOURNAL: Journal of Cell Biology 137 (3): p685-701 1997 1997

ISSN: 0021-9525

DOCUMENT TYPE: Article

RECORD TYPE: Abstract

LANGUAGE: English

ABSTRACT: %%%Laminin%%% %%%trimers%%% composed of alpha, beta, and gamma chains are major components of basal laminae (BLs) throughout the body. To date, three alpha chains (alpha-1-3) have been shown to assemble into at least seven heterotrimers (called laminins 1-7). Genes encoding two additional alpha chains (alpha-4 and alpha-5) have been cloned, but little is known about their expression, and their protein products have not been identified. Here we generated antisera to recombinant alpha-4 and alpha-5 and used them to identify authentic proteins in tissue extracts. Immunoprecipitation and immunoblotting showed that alpha-4 and alpha-5 assemble into four novel %%%laminin%%% heterotrimers (laminins 8-11: alpha-4-beta-1-gamma-1, alpha-4-beta-2-gamma-1, alpha-5-beta-1-gamma-1, and alpha-5-beta-2-gamma-1, respectively). Using a panel of nucleotide and antibody probes, we surveyed the expression of alpha-1-5 in murine tissues. All five chains were expressed in both embryos and adults, but each was distributed in a distinct pattern at both RNA and protein levels. Overall, alpha-4 and alpha-5 exhibited the broadest patterns of expression, while expression of alpha-1 was the most restricted. Immunohistochemical analysis of kidney, lung, and heart showed that the alpha chains were confined to extracellular matrix and, with few exceptions, to BLs. All developing and adult BLs examined contained at least one %%%alpha%%% %%%chain%%%, all alpha chains were present in multiple BLs, and some BLs contained two or three alpha chains. Detailed analysis of developing kidney revealed that some individual BLs,



including those of the tubule and glomerulus, changed in laminin chain composition as they matured, expressing up to three different  $\alpha$  chains and two different beta chains in an elaborate and dynamic progression. Interspecific backcross mapping of the five  $\alpha$  chain genes revealed that they are distributed on four mouse chromosomes. Finally, we identified a novel full-length  $\alpha$ -3 isoform encoded by the Lama3 gene, which was previously believed to encode only truncated chains. Together, these results reveal remarkable diversity in BL composition and complexity in BL development.

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18242124 BIOSIS NO.: 200500149189

Induction, differentiation, and remodeling of blood vessels after transplantation of Bcl-2-transduced endothelial cells

AUTHOR: Enis David R; Shepherd Benjamin R; Wang Yinong; Qasim Asif; Shanahan Catherine M; Weissberg Peter L; Kashgarian Michael; Pober Jordan S (Reprint); Schechner Jeffrey S

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JOURNAL: Proceedings of the National Academy of Sciences of the United States of America 102 (2): p425-430 January 11, 2005 2005

MEDIUM: print

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LANGUAGE: English

ABSTRACT: Implants of collagen-fibronectin gels containing Bcl-2-transduced human umbilical vein endothelial cells (Bcl-2-HUVECs) induce the formation of human endothelial cell (EC)/murine vascular smooth muscle cell (VSMC) chimeric vessels in immunodeficient mice. Microfil casting of the vasculature 60 d after implantation reveals highly branched microvascular networks within the implants that connect with and induce remodeling of conduit vessels arising from the abdominal wall circulation. Approximately 85% of vessels within the implants are lined by Bcl-2-positive human ECs expressing VEGFR1, VEGFR2, and Tie-2, but not integrin  $\alpha$ v $\beta$ 3. The human ECs are seated on a well formed human laminin/collagen IV-positive basement membrane, and are surrounded by mouse VSMCs expressing SM- $\alpha$  actin, SM myosin, SM22 $\alpha$ , and calponin, all markers of contractile function. Transmission electron microscopy identified well formed EC-EC junctions, chimeric arterioles with concentric layers of contractile VSMC, chimeric capillaries surrounded by pericytes, and chimeric venules. Bcl-2-HUVEC-lined vessels retain 70-kDa FITC-dextran, but not 3-kDa dextran; local histamine rapidly induces leak of 70-kDa FITC-dextran or India ink. As in skin, TNF induces E-selectin and vascular cell adhesion molecule 1 only on venular ECs, whereas intercellular adhesion molecule-1 is up-regulated on all human ECs. Bcl-2-HUVEC implants are able to engraft within and increase perfusion of ischemic mouse gastrocnemius muscle after femoral artery ligation. These studies show that cultured Bcl-2-HUVECs can differentiate into arterial,

venular, and capillary-like ECs when implanted in vivo, and induce arteriogenic remodeling of the local mouse vessels. Our results support the utility of differentiated EC transplantation to treat tissue ischemia.

7/7/2

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17810043 BIOSIS NO.: 200400190800

Signals regulating tendon formation during chick embryonic development.

AUTHOR: Edom-Vovard Frederique; Duprez Delphine (Reprint)

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JOURNAL: Developmental Dynamics 229 (3): p449-457 March 2004 2004

MEDIUM: print

ISSN: 1058-8388 (ISSN print)

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RECORD TYPE: Abstract

LANGUAGE: English

ABSTRACT: Tendons are %collagen%-rich structures that link muscle to cartilage. By using quail-chick %chimeras%, it has been shown that tendon and cartilage cells originate from the same mesodermic compartment, which is distinct from that giving rise to muscle cells. Axial tendons originate from the sclerotomal compartment, and limb tendons originate from the lateral plate, whereas axial and limb muscles derive from dermomyotomes. Despite these different embryologic origins, muscle and tendon morphogenesis occurs in close spatial and temporal association. Facilitated by the distinct embryologic origin of myogenic and tendon cells, surgical studies in the avian embryo have highlighted interactions between tendons and muscles, during embryonic development. However, these interactions seem to differ between axial and limb levels. The molecular mechanisms underlying muscle and tendon interactions have been shown recently to involve different members of the fibroblast growth factor family. This review covers the available data on the early steps of tendon formation in the limb and along the primary axis. The relationship with muscle morphogenesis will be highlighted.

7/7/3

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17792924 BIOSIS NO.: 200400160265

The role of the cytoplasmic domain of the alpha3 - subunit of the alpha3beta1 integrin in adhesion, proliferation and neurite outgrowth of PC12 cells.

AUTHOR: Mechai N (Reprint); Reutter W (Reprint); Danker K (Reprint)

AUTHOR ADDRESS: Fachbereich Humanmedizin, Institut für Molekularbiologie und Biochemie, Berlin, Germany\*\*Germany

JOURNAL: Society for Neuroscience Abstract Viewer and Itinerary Planner 2003 pAbstract No. 34.26 2003 2003

MEDIUM: e-file

CONFERENCE/MEETING: 33rd Annual Meeting of the Society of Neuroscience New

Orleans, LA, USA November 08-12, 2003; 20031108  
SPONSOR: Society of Neuroscience  
DOCUMENT TYPE: Meeting; Meeting Abstract  
RECORD TYPE: Abstract  
LANGUAGE: English

ABSTRACT: Integrins present large transmembrane proteins, consisting of an  $\alpha$  and a  $\beta$  chain. they are receptors for ECM components including fibronectin, laminin and collagen, which are specifically recognized at sites often containing the tripeptide RGD. The cytoplasmic domains of integrins are linked to the actin cytoskeleton by linker molecules such as talin, vinculin and  $\alpha$ -actinin. Signal transduction through integrins occurs in two directions: from the extracellular microenvironment into the cell cytoplasm (outside-in signaling) and from the cytoplasm to the extracellular domain of the receptor (inside-out signaling). Integrins play an important role in controlling various steps in the signaling pathways that regulate processes as diverse as adhesion, proliferation, or neurite outgrowth. To investigate the integrin-dependent mechanisms in this process, we take advantage of the PC12 cell line that express integrin receptors for collagen and laminin. In our study we elucidate the contribution of the cytoplasmic domain of the  $\alpha 3$ -integrin in cell adhesion and neurite outgrowth. NGF-primed PC12 cells were transiently transfected with cDNA containing a chimeric receptor consisting of the extracellular and transmembrane domains of the small subunit of the human interleukin-2 receptor (CD25) fused to the  $\alpha 3A$ -integrin cytoplasmic domain. The overexpression of this chimera does not effect cell adhesion to collagen-IV, laminin-1, laminin-5 rich matrix, fibronectin and poly-L-Lysine while the matrix-dependent cell proliferation of the transfectants was increased only on laminin-1, laminin-5 rich matrix and on collagen-IV. The cell morphology of the transfected NGF-primed cells was also changed on both laminin isoforms, this cells remained unspread with no neurites whereas the control cells differentiated into sympathetic-like neurons.

7/7/4

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17755899 BIOSIS NO.: 200400126656

Disruption of integrin/extracellular matrix interactions enhances the beta-adrenergic regulation of the cardiac L-type calcium current.

AUTHOR: Cheng Qi (Reprint); Ross Robert S; Walsh Kenneth B (Reprint)

AUTHOR ADDRESS: Pharmacology, Physiology and Neuroscience, University of South Carolina, Columbia, SC, USA\*\*USA

JOURNAL: Biophysical Journal 86 (1): p128a January 2004 2004

MEDIUM: print

CONFERENCE/MEETING: 48th Annual Meeting of the Biophysical Society  
Baltimore, MD, USA February 14-18, 2004; 20040214

SPONSOR: Biophysical Society

ISSN: 0006-3495 (ISSN print)

DOCUMENT TYPE: Meeting; Meeting Abstract

RECORD TYPE: Abstract

LANGUAGE: English

ABSTRACT: Integrins are a family of cell surface receptors that link the

extracellular matrix (ECM) to the cellular cytoskeleton. The goal of this study was to determine the importance of the integrin beta1 subunit in regulating cardiac L-type Ca<sup>2+</sup> channel function. Methods: rat ventricular myocytes were cultured on %collagen% membranes and infected with adenovirus expressing a %chimeric% protein consisting of the cytoplasmic tail domain of the beta1A integrin and the extracellular/transmembrane domains of the interleukin-2 receptor (AdTAC-beta1A). Expression of beta integrin tails disrupts integrin signaling and prevents normal cell adhesion. Ventricular myocytes were also isolated from mice with a targeted disruption of beta1 integrin gene (beta1Flox/Flox/MLC2v+/Cre) and plated on %laminin%-coated coverslips. Results: when compared with myocytes infected with control virus, AdTAC-beta1A infection did not produce any significant change in the current versus voltage relationship of the whole-cell Ca<sup>2+</sup> current (ICa) or the kinetics of ICa decay. Application of the beta-adrenergic receptor agonist isoproterenol produced over a 90% increase in ICa in control cells. Surprisingly, expression of TAC-beta1A was associated with an augmentation (160% increase) in the Ca<sup>2+</sup> channel response to isoproterenol. Addition of acetylcholine decreased the beta-adrenergic-regulated ICa by 60% in both control and AdTAC-beta1A infected cells. Currents measured in myocytes isolated from beta1Flox/Flox/MLC2v+/Cre mice also demonstrated a greater response to isoproterenol (122+-13% increase) when compared with cells from control, beta1Flox/Flox mice (79+-10% increase). Conclusion: disruption of integrin/ECM interactions enhances the beta-adrenergic regulation of ICa.

7/7/5

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17680133 BIOSIS NO.: 200400047663

EWI-2 regulates alphabeta1 integrin-dependent cell functions on %laminin%-5.

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JOURNAL: Journal of Cell Biology 163 (5): p1167-1177 December 8, 2003 2003

MEDIUM: print

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LANGUAGE: English

ABSTRACT: EWI-2, a cell surface immunoglobulin SF protein of unknown function, associates with tetraspanins CD9 and CD81 with high stoichiometry. Overexpression of EWI-2 in A431 epidermoid carcinoma cells did not alter cell adhesion or spreading on %laminin%-5, and had no effect on reaggregation of cells plated on %collagen% I (alpha2beta1 integrin ligand). However, on %laminin%-5 (alpha3beta1 integrin ligand), A431 cell reaggregation and motility functions were markedly impaired. Immunodepletion and reexpression experiments revealed that tetraspanins CD9 and CD81 physically link EWI-2 to alpha3beta1 integrin, but not to other integrins. CD81 also controlled EWI-2 maturation and cell surface localization. EWI-2 overexpression not only suppressed cell

migration, but also redirected CD81 to cell filopodia and enhanced alpha3beta1-CD81 complex formation. In contrast, an EWI-2 %%%chimeric%%% mutant failed to suppress cell migration, redirect CD81 to filopodia, or enhance alpha3beta1-CD81 complex formation. These results show how laterally associated EWI-2 might regulate alpha3beta1 function in disease and development, and demonstrate how tetraspanin proteins can assemble multiple nontetraspanin proteins into functional complexes.

7/7/6

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17611650 BIOSIS NO.: 200300580369

A functional analysis of the *C. albicans* Als family of proteins.

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JOURNAL: Abstracts of the Interscience Conference on Antimicrobial Agents and Chemotherapy 43 p438 2003 2003

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CONFERENCE/MEETING: 43rd Annual Interscience Conference on Antimicrobial Agents and Chemotherapy Chicago, IL, USA September 14-17, 2003; 20030914

SPONSOR: American Society for Microbiology

DOCUMENT TYPE: Meeting; Meeting Abstract

RECORD TYPE: Abstract

LANGUAGE: English

ABSTRACT: Background: The *C. albicans* Als family of proteins comprises at least 9 members that share structural homology. Two members of this family, Als1p and Als5p, have been shown to mediate adherence to host constituents, but little is known about the function of other members of this protein family. We therefore used heterologous expression of Als proteins in the non-adherent *Saccharomyces cerevisiae* to characterise their adhesive function. Methods: Putative ALS genes were identified by BLAST searches of the Stanford *C. albicans* genome database. These genes were then cloned by high fidelity PCR, and expressed in *S. cerevisiae*. Strains expressing Als proteins were then assayed for adhesion to biological substrates including %%%laminin%%%, %%%collagen%%%, fibronectin, vascular endothelial cells and oral epithelial cells. Results: ALS1,3,5,6,7 and 9 were cloned and expressed in *S. cerevisiae*. Different Als proteins displayed specific patterns of substrate specific adherence. Clones expressing Als1,3 or 5p were adherent to all substrates tested, although with varying degrees of affinity. In contrast, Als6p expressing strains adhered only to %%%collagen%%%, Als9p to %%%laminin%%%, and Als7p strains failed to adhere to any of the substrates tested. To determine which domain was responsible for Als5p mediated substrate specific adherence, we constructed %%%chimeric%%% fusions of Als5p and Als6p in which the N-terminal half of one Als5p was fused to the C-terminal half of the other. Analysis of the adherence of these clones confirmed that substrate specific adherence was dependent on N-terminal sequences. Conclusions: The Als protein family comprises a group of adhesins capable of binding multiple biologically relevant substrates. This substrate specific adherence is likely mediated by the N-terminus of Als proteins. The complex and overlapping substrate specificity patterns displayed by Als proteins provides this organism with an array of adhesins capable of exploiting multiple ecological niches.

7/7/7

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17532951 BIOSIS NO.: 200300490608

Sufficiency of the reactive site loop of maspin for induction of cell-matrix adhesion and inhibition of cell invasion. Conversion of ovalbumin to a maspin-like molecule.

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JOURNAL: Journal of Biological Chemistry 278 (34): p31796-31806 August 22, 2003 2003

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DOCUMENT TYPE: Article

RECORD TYPE: Abstract

LANGUAGE: English

ABSTRACT: Maspin, an ov-serpin, inhibits tumor invasion and induces cell adhesion to extracellular matrix molecules. Here, we use maspin/ovalbumin %%chimeric%% proteins and the maspin reactive site loop (RSL) peptide to characterize the role of the RSL in maspin-mediated functions. Replacement of the RSL plus the C-terminal region or the RSL alone of maspin with that of ovalbumin resulted in the loss of the stimulatory effect on adhesion of corneal stromal cells to type I %%collagen%%, fibronectin, and %%laminin%% and of mammary carcinoma MDA-MB-231 cells to fibronectin. Maspin with ovalbumin as the C-terminal region retained activity, suggesting the maspin C-terminal polypeptide is not required. An R340Q mutant retained full maspin activity; however, an R340A mutant lost activity. This indicates the arginine side chain at the putative P1 site forms a hydrogen bond and not an ionic bond. The RSL peptide (P10-P5', amino acids 330-345) alone induced cell-matrix adhesion of mammary carcinoma cells and corneal stromal cells and inhibited invasion of the carcinoma cells. Substitution of the RSL of ovalbumin with that of maspin converted inactive ovalbumin into a fully active molecule. Maspin bound specifically to the surface of the mammary carcinoma cells with a  $K_d$  of  $367 \pm 67$  nM and  $32.0 \pm 2.2 \times 10^6$  binding sites/cell. The maspin RSL peptide inhibited binding, suggesting the RSL is involved in maspin binding to cells. Sufficiency of the maspin RSL for activity suggests the mechanism by which maspin regulates cell-matrix adhesion and tumor cell invasion does not involve the serpin mechanism of protease inhibition.

7/7/8

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17302780 BIOSIS NO.: 200300261424

Crystal structure of the  $\alpha\beta$  integrin I domain in complex with an antibody Fab fragment.

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JOURNAL: Journal of Molecular Biology 327 (5): p1031-1041 11 April, 2003  
2003  
MEDIUM: print  
ISSN: 0022-2836 (ISSN print)  
DOCUMENT TYPE: Article  
RECORD TYPE: Abstract  
LANGUAGE: English

ABSTRACT: The alphalbetal (VLA-1) integrin is a cell-surface receptor for  
%%collagen%% and %%laminin%% and has been implicated in biological  
pathways involved in several pathological processes. These processes may  
be inhibited by the monoclonal antibody AQC2, which binds with high  
affinity to human alphalbetal integrin. To understand the structural  
basis of the inhibition we determined the crystal structure of the  
complex of a %%chimeric%% rat/human I domain of the alphalbetal  
integrin and the Fab fragment of humanized AQC2 antibody. The structure  
of the complex shows that the antibody blocks the %%collagen%% binding  
site of the I domain. An aspartate residue, from the CDR3 loop of the  
antibody heavy chain, coordinates the MIDAS metal ion in a manner similar  
to that of a glutamate residue from %%collagen%%. Substitution of the  
aspartate residue by alanine or arginine results in significant reduction  
of antibody binding affinity. Interestingly, although the mode of metal  
ion coordination resembles that of the open conformation, the I domain  
maintains an overall closed conformation previously observed only for  
unliganded I domains.

7/7/9

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16256569 BIOSIS NO.: 200100428408  
Differential gene expression during capillary morphogenesis in 3D  
%%collagen%% matrices: Regulated expression of genes involved in  
basement membrane matrix assembly, cell cycle progression, cellular  
differentiation and G-protein signaling  
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JOURNAL: Journal of Cell Science 114 (15): p2755-2773 August, 2001 2001  
MEDIUM: print  
ISSN: 0021-9533  
DOCUMENT TYPE: Article  
RECORD TYPE: Abstract  
LANGUAGE: English

ABSTRACT: We have performed a screening analysis of differential gene  
expression using a defined in vitro model of human capillary tube  
formation. Gene array, differential display and cDNA library screening  
were used to identify both known and novel differentially expressed  
genes. Major findings include: the upregulation and functional importance  
of genes associated with basement membrane matrix assembly; the

upregulation of growth factors, transcription factors, anti-apoptotic factors, markers of endothelial cell differentiation, JAK-STAT signalling molecules, adhesion receptors, proteinase inhibitors and actin regulatory proteins; and expression changes consistent with inhibition of cell cycle progression, increased cholesterol biosynthesis, decreased ubiquitin-proteasome mediated degradation, and activation of G-protein signaling pathways. Using DNA microarray analysis, the most induced genes at 8, 24 and 48 hours compared with those at 0 hours were jagged-1, stanniocalcin and angiopoietin-2, whereas the most repressed genes were connective tissue growth factor, fibulin-3 and RGS-5. In addition, the full length coding sequence of two novel regulated capillary morphogenesis genes (CMGs) are presented. CMG-1 encodes a predicted intracellular 65 kDa protein with coiled-coil domains. A CMG-1-green fluorescent protein (GFP) **%%chimera%%** was observed to target to an intracellular vesicular compartment. A second novel gene, CMG-2, was found to encode a predicted intracellular protein of 45 kDa containing a transmembrane segment and a CMG-2-GFP **%%chimera%%** was observed to target to the endoplasmic reticulum. A recombinant portion of CMG-2 was found to bind **%%collagen%%** type IV and **%%laminin%%**, suggesting a potential role in basement membrane matrix synthesis and assembly. These data further elucidate the genetic events regulating capillary tube formation in a 3D matrix environment.

7/7/10

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16225414 BIOSIS NO.: 200100397253

Functional comparison of the alpha3A and alpha3B cytoplasmic domain variants of the chicken alpha3 integrin subunit

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JOURNAL: Experimental Cell Research 268 (1): p45-60 August 1, 2001 2001

MEDIUM: print

ISSN: 0014-4827

DOCUMENT TYPE: Article

RECORD TYPE: Abstract

LANGUAGE: English

ABSTRACT: Integrin alpha3beta1 can be alternatively spliced to generate alpha3A and alpha3B cytoplasmic domain variants that are conserved among vertebrates. To identify distinct functions of these variants, we transfected cells with intact alpha3 integrins or **%%chimeric%%** receptors. alpha3Abeta1 and alpha3Bbeta1 each localized to focal contacts in keratinocytes on an extracellular matrix rich in **%%laminin%%**-5, to which both are known to bind with high affinity. However, alpha3B accumulated intracellularly in keratinocytes on **%%collagen%%**, suggesting that **%%laminin%%** binding may stabilize alpha3Bbeta1 surface expression. Neither alpha3 cytoplasmic domain affected recruitment of **%%chimeric%%** alpha5 integrins to fibronectin-induced focal contacts, and either substituted for the alpha5 cytoplasmic domain in alpha5beta1-mediated cell migration. However, the alpha5/alpha3B **%%chimera%%** localized to cell-cell borders in MDCK or CHO cells to a lesser extent than did the alpha5/alpha3A **%%chimera%%**. To determine



whether the alpha3 cytoplasmic domains conferred distinct localization to a nonintegrin protein, we transfected cells with interleukin-2 receptor (IL-2R) %%%chimeras%%% containing the alpha3 cytoplasmic domains. The IL-2R/alpha3A %%%chimera%%% was expressed efficiently on the cell surface, while the IL-2R/alpha3B %%%chimera%%% accumulated intracellularly. Our findings suggest that the alpha3B cytoplasmic domain harbors a retention signal that is regulated in an intact integrin and can alter cell surface expression and distribution of alpha3beta1.

7/7/11

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15722714 BIOSIS NO.: 200000441027

In vitro studies on PGC or PGC-like cells in cultured yolk sac cells and embryonic stem cells of the mouse

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JOURNAL: Archives of Histology and Cytology 63 (3): p229-241 July, 2000 2000

MEDIUM: print

ISSN: 0914-9465

DOCUMENT TYPE: Article

RECORD TYPE: Abstract

LANGUAGE: English

ABSTRACT: The present study aims: 1) to determine those conditions which promote the proliferation of primordial germ cells (PGCs) of the migratory phase in the yolk sac; and 2) to examine the effects of yolk sac cells as a feeder layer-under the conditions mentioned above-upon the embryonic stem (ES) cells (R1) with high potential for entering the germ line in vivo in %%%chimeras%%%. In murine yolk sac cells obtained on Day 10.5-11.5 of pregnancy and cultured in a modified Dulbecco's modified Eagle's medium (DMEM-plus/20: the postfix represents the concentration of FBS added in percentage), many cells exhibited strong immunoreactivities to the monoclonal antibodies 4C9 and 2C9 which are known to react with PGC specifically. Both the 4C9- and the 2C9-positive cells were sensitive to the treatment with busulfan added in vitro, supporting the supposition that they were PGCs. The respective numbers of the 4C9- and the 2C9-positive cells increased approximately 4 and 12 times when they were cultured in DMEM-plus/20 fortified with SCF, LIF, bFGF and TNF-alpha (DMEM-NT/20). When the R1 cells were cultured in the yolk sac-conditioned DMEM-NT/20 medium on the %%%laminin%%% substratum, the entire colonies were faintly stained with 4C9 but not with 2C9. At times solitary ES cells migrated out from the colonies, and reacted strongly with 4C9. When yolk sac cells and R1 cells were cultured on the two sides of a %%%collagen%%%coated membrane, the yolk sac cells being feeder cells, some R1 cell colonies were intensely stained as a whole with either the 4C9 or the 2C9 antibody, suggesting that these colonies might be composed of cells clonally derived from stem cells which either had been destined to become the germ line cells or had already acquired cellular characteristics close to PGCs. It was tentatively concluded that the R1 cell population contained, as judged from the immunoreactivities,

germ-cell-like cells, and that the yolk sac cells and/or their secretory products might facilitate the proliferation of, or the conversion of R1 cells to, the germ-cell-like cells.

7/7/12

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15625184 BIOSIS NO.: 200000343497

VLA-4 (alpha4beta1) engagement defines a novel activation pathway for beta2 integrin-dependent leukocyte adhesion involving the urokinase receptor

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JOURNAL: Blood 96 (2): p506-513 July 15, 2000 2000

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LANGUAGE: English

ABSTRACT: During acute inflammatory processes, beta2 and beta1 integrins sequentially mediate leukocyte recruitment into extravascular tissues. We studied the influence of VLA-4 (very late antigen-4) (alpha4beta1) engagement on beta2 integrin activation-dependent cell-to-cell adhesion. Ligation of VLA-4 by the soluble %%chimera%% fusion product vascular cell adhesion molecule-1 (VCAM-1)-Fc or by 2 anti-CD29 (beta1 chain) monoclonal antibodies (mAb) rapidly induced adhesion of myelomonocytic cells (HL60, U937) to human umbilical vein endothelial cells (HUVECs). Cell adhesion was mediated via beta2 integrin (LFA-1 and Mac-1) activation: induced adhesion to HUVECs was inhibited by blocking mAbs anti-CD18 (70%-90%), anti-CD11a (50%-60%), or anti-CD11b (60%-70%). Adhesion to immobilized ligands of beta2 integrins (intercellular adhesion molecule-1 (ICAM-1), fibrinogen, keyhole limpet hemocyanin) as well as to ICAM-1-transfected Chinese hamster ovary cells, but not to ligands of beta1 integrins (VCAM-1, fibronectin, %%laminin%%, and %%collagen%%), was augmented. VCAM-1-Fc binding provoked the expression of the activation-dependent epitope CBRM1/5 of Mac-1 on leukocytes. Clustering of VLA-4 through dimeric VCAM-1-Fc was required for beta2 integrin activation and induction of cell adhesion, whereas monovalent VCAM-1 or Fab fragments of anti-beta1 integrin mAb were ineffective. Activation of beta2 integrins by alpha4beta1 integrin ligation (VCAM-1-Fc or anti-beta1 mAb) required the presence of urokinase receptor (uPAR) on leukocytic cells, because the removal of uPAR from the cell surface by phosphatidylinositol-specific phospholipase C reduced cell adhesion to less than 40%. Adhesion was reconstituted when soluble recombinant uPAR was allowed to reassociate with the cells. Finally, VLA-4 engagement by VCAM-1-Fc or anti-beta1 integrin mAb induced uPAR-dependent adhesion to immobilized vitronectin as well. These results elucidate a novel activation pathway of beta2 integrin-dependent cell-to-cell adhesion that requires alpha4beta1 integrin ligation for initiation and uPAR as activation transducer.

7/7/13

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15483698 BIOSIS NO.: 200000202011

Formation of hemidesmosome-like structures in the absence of ligand binding by the alpha6beta4 integrin requires binding of HD1/plectin to the cytoplasmic domain of the beta4 integrin subunit

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JOURNAL: Journal of Cell Science 113 (6): p963-973 March, 2000 2000

MEDIUM: print

ISSN: 0021-9533

DOCUMENT TYPE: Article

RECORD TYPE: Abstract

LANGUAGE: English

ABSTRACT: Hemidesmosomes are adhesion structures that mediate anchorage of epithelial cells to the underlying basement membrane. We have previously shown that the alpha6beta4 integrin can induce the assembly of these multi-protein structures independent of binding to its ligand %%%laminin%%%5 (ligand-independent formation of hemidesmosomes). Our results suggested a role for HD1/plectin, which binds to the cytoplasmic domain of the beta4 integrin subunit, in controlling the clustering of hemidesmosomal components at the basal side of the cell. Using keratinocytes derived from patients lacking HD1/plectin, we now show that ligand-independent formation of hemidesmosomal clusters indeed requires HD1/plectin, in contrast to the ligand-dependent assembly of hemidesmosomes. No clustering of the alpha6beta4 integrin, or of the bullous pemphigoid antigens BP180 and BP230, was seen when HD1/plectin-deficient keratinocytes were plated on fibronectin or type IV %%%collagen%%%. In beta4-deficient keratinocytes, expression of an interleukin 2 receptor (IL2R) transmembrane %%%chimera%%% containing the beta4 cytoplasmic tail with the mutation R1281W, which abrogates HD1/plectin binding, resulted in a diffuse distribution of the %%%chimeric%%% receptor. In contrast, a beta4R1281W mutant that can associate with alpha6 and bind ligand, was found to be directed to the basal surface of the cells, at sites where %%%laminin%%%5 was deposited. In addition, this mutant induced clustering of BP180 and BP230 at these sites. Together, these results show that the formation of hemidesmosomes requires binding of either ligand or HD1/plectin to the beta4 integrin subunit. Intriguingly, we found that IL2R/beta4 %%%chimeras%%% become localized in pre-existing hemidesmosomes of HD1/plectin-deficient keratinocytes, and that this localization requires a domain in the beta4 cytoplasmic tail that is also required for HD1/plectin binding (residues 1115-1356). Because this part of beta4 lacks the BP180 binding site, and since we show in this study that it is unable to interact with the same part on another beta4 molecule, we suggest that the %%%chimera%%% becomes incorporated into hemidesmosomes of HD1/plectin-deficient keratinocytes by interacting with an as yet unidentified hemidesmosomal component.

7/7/14

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13740375 BIOSIS NO.: 199799374435

Skin replacement using %%%chimeric%% (allogeneic-syngeneic) cultured epidermal sheets

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JOURNAL: M-S (Medecine Sciences) 12 (12): p1370-1377 1996 1996

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RECORD TYPE: Abstract

LANGUAGE: French

ABSTRACT: Skin is the main interface between the organism and the environment. This organ is only a few millimetres thick, but still constitutes the body's largest organ. It is particularly vulnerable to environment-induced traumas. Extensive skin loss such as in burns causes serious complications and may lead to death if not prevented by early wound closure. In extensively burned patients, donor site availability for meshed skin autografting remains the limiting factor for wound coverage and skin replacement. The concept of using allogeneic skin for burn treatment remains an interesting one. However, full engraftment does not occur since these grafts remain immunogenic. Recently, cultured epithelial sheets have been used as an adjunct therapy. Human epidermal cells have been grown in vitro and successfully used for grafting onto skin defects and extensive burn wounds. However, this new therapeutic approach has the disadvantage of requiring delays of up to 4 to 5 weeks to allow epithelial cells to grow in vitro. Some research groups have tried to overcome this drawback by grafting allogeneic epidermal sheets devoid of Langerhans cells. However, strong arguments based on immunological mechanisms have prompted doubts about the permanent survival of these cultured epidermal allografts. Since cultured epithelium allografting proved impossible, as well as the fact that the cutaneous tissues of extensively burned patients have to be replaced quickly and permanently, using an experimental model, we devised, a new culture technology using allogeneic and syngeneic epithelial cells for %%%chimeric%% graftable sheet production. Indeed, 14 days postgrafting, %%%chimeric%% implants (50%Balb/c-50%C3H/HeN, 25%Balb/c-75%C3H/HeN grafted onto Balb/c adult mice) showed the same percentages of implantation success (gt 80%) as for isografts. Histological studies revealed a well-organized cutaneous tissue containing basal and suprabasal cell layers. These histological observations were confirmed by results showing the presence of basement membrane proteins (%%laminin%%, and type IV %%collagen%%). The %%%chimeric%% results were comparable to those obtained with isografts, meanwhile allografts showed complete degradation, indicating implant rejection. Thirty days postgrafting, immunohistological studies revealed that %%%chimeric%% implants allowed epidermis regeneration, and that these %%%chimeric%% epithelial sheets showed no sign of rejection over time, while their allogeneic keratinocytes seemed to be passively "removed" from the implants. Clinically, the use of this %%%chimeric%% culture method (mixture of allogeneic and autologous keratinocyte populations) for large burn wound treatment could be a significant therapeutic advance. It may reduce by at least 50% the previously described delay for epidermal culture, and significantly lower the cost of burn management during patient hospitalization. Also, since the ultimate aim in allogeneic transplantation is to achieve immunological tolerance between donors and recipients, this %%%chimeric%% culture approach may provide ways to

study tolerance phenomena in cutaneous tissues.

7/7/15

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13405671 BIOSIS NO.: 199699039731

Permanent skin replacement using %%%chimeric%%% epithelial cultured sheets comprising xenogeneic and syngeneic keratinocytes

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JOURNAL: Transplantation (Baltimore) 61 (9): p1290-1300 1996 1996

ISSN: 0041-1337

DOCUMENT TYPE: Article

RECORD TYPE: Abstract

LANGUAGE: English

ABSTRACT: The present study was undertaken to evaluate the possibility of permanent skin replacement using %%%chimeric%%% xenogeneic-syngeneic graftable sheets previously obtained in vitro. Newborn (1 to 3 days old) BALB/c and human keratinocytes were isolated and cocultured in different ratios as follows: 50% BALB/c to 50% human and 25% BALB/c to 75% human keratinocytes. Four to 5 days after culture and prior to their grafting, all %%%chimeric%%% sheets contained both cell types in ratios similar to those used to seed the initial %%%chimeric%%% cultures. Fourteen and 30 days after %%%chimeric%%% sheet grafting onto BALB/c mice dorsum, the newly generated cutaneous tissue showed a histologically well-organized epidermis presenting basal and suprabasal cell layers. Cutaneous cells in these structures secreted %%%laminin%%% and type IV %%%collagen%%% in blood vessels, and at ground level of the dermoepidermal junction there were signs of physiologically active skin. Cell phenotyping revealed the presence of only syngeneic keratinocytes, whereas xenogeneic cells were passively eliminated without a total rejection of the %%%chimeric%%% implant. This selective and passive elimination of xenogeneic keratinocytes went through cellular and humoral immunity activation. Data suggest that this %%%chimeric%%% culture method can be used for cutaneous therapies such as large congenital nevi, skin ulcers, and extensively burned skin. Indeed, for large third-degree wounded skin treatment, this culture method may shorten the time (4-5 weeks) needed for cell growth and graftable sheet production. Moreover, since the ultimate aim in allogeneic and xenogeneic transplantation is to achieve an immunological acceptance and tolerance to these foreign tissues, the %%%chimeric%%% culture approach may provide ways to lighten tolerance phenomena on cutaneous tissue.

7/7/16

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13366683 BIOSIS NO.: 199699000743

Activated conformations of very late activation integrins detected by a group of antibodies (HUTS) specific for a novel regulatory region (335-425) of the common beta-1 chain

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JOURNAL: Journal of Biological Chemistry 271 (19): p11067-11075 1996 1996  
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RECORD TYPE: Abstract  
LANGUAGE: English

ABSTRACT: The very late activation antigens (VLA) or beta-1 integrins mediate cell attachment to different extracellular matrix proteins and intercellular adhesions. The ligand binding activity of these adhesion receptors is not constitutive and can be regulated by temperature, presence of extracellular divalent cations, stimulatory monoclonal antibodies (mAbs), and cellular activation. We have generated three novel mAbs, HUTS-4, HUTS-7, and HUTS-21, recognizing specific epitopes on the common beta-1 subunit (CD29) of VLA integrins whose expression correlates with the ligand binding activity of these heterodimeric glycoproteins. This correlation has been demonstrated for several integrin heterodimers in different cell systems using a variety of extracellular and intracellular stimuli for integrin activation. Thus, the presence of micromolar concentrations of extracellular Mn-2+, preincubation with the activating anti-beta-1 mAb TS2/16, and cell treatment with phorbol esters or calcium ionophores, induced the expression of the HUTS beta-1 epitopes on T lymphoblasts. Using a panel of human-mouse beta-1 %%%chimeric%%% molecules, we have mapped these epitopes to the 355-425 sequence of the beta-1 polypeptide. This segment represents therefore a novel regulatory region of beta-1 that is exposed upon integrin activation. Interestingly, binding of HUTS mAbs to partially activated VLA integrins results in maximal activation of these adhesion receptors and enhancement of cell adhesion to beta-1 integrin ligands %%%collagen%%%, %%%laminin%%%, and fibronectin.

7/7/17  
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13224505 BIOSIS NO.: 199698692338  
Development of chicken aortic smooth muscle: Expression of cytoskeletal and basement membrane proteins defines two distinct cell phenotypes emerging from a common lineage  
AUTHOR: Yablonka-Reuveni Zipora (Reprint); Schwartz Stephen M; Christ Bodo  
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JOURNAL: Cellular and Molecular Biology Research 41 (4): p241-249 1995 1995  
ISSN: 0968-8773  
DOCUMENT TYPE: Article  
RECORD TYPE: Abstract  
LANGUAGE: English

ABSTRACT: We describe our studies on the characterization of the cell phenotypes in the wall of the aortic-arch-derived arteries from "late" chicken embryos. Using immunocytochemistry with antibodies against smooth muscle cytoskeletal and basement membrane proteins, we show that the smooth muscle of the aortic-arch-derived arteries from 13- to 19-d-old

embryos contains two cell phenotypes organized in interchanging lamellae. One cell phenotype (lamellar cells), but not the other cell phenotype (interlamellar cells), expresses the cytoskeletal proteins desmin and alpha smooth muscle actin (alpha-SMactin). Both cell phenotypes express the cytoskeletal protein vimentin. Furthermore, the lamellar cells but not the interlamellar cells are surrounded by the basement membrane proteins %laminin% and %collagen% type IV. Performing quail-chick transplantation experiments and using a quail specific antibody, we show that both lamellar and interlamellar cells in the "aortic arches" of a 15-d-old %chimeric% embryo are derived from neural crest cells. We conclude that the aortic smooth muscle cells from "late" chicken embryos consist of two distinct cell phenotypes which are derived from a common lineage.

7/7/18

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13175972 BIOSIS NO.: 199698643805

Type IV %collagen%-binding proteins of neutrophils: Possible involvement of L-selectin in the neutrophil binding to type IV %collagen%

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JOURNAL: Blood 87 (1): p365-372 1996 1996

ISSN: 0006-4971

DOCUMENT TYPE: Article

RECORD TYPE: Abstract

LANGUAGE: English

ABSTRACT: To isolate type IV %collagen%-binding proteins, 125I-labeled human-neutrophil extracts were chromatographed on a type IV %collagen%-Sepharose column. The affinity chromatography-separated fraction contained the four radioactive proteins with apparent molecular masses of 28, 49, 67, and 95 kD on sodium dodecyl sulfate-polyacrylamide gel electrophoresis. Western blot analysis indicated that the 95-kD proteins contained both L-selectin and nonspecific cross-reacting antigen 90 (NCA90), and that the 67-kD protein was the 67-kD elastin/%laminin%-binding protein (67BP). The data obtained with the type IV %collagen%-affinity chromatography and the immunoaffinity chromatographies using anti-L-selectin and anti-NCA90 monoclonal antibodies (MoAbs) have shown that L-selectin is closely associated with 67BP and the 49-kD protein, and that NCA90 is associated with 67BP, the 28-kD and 49-kD proteins. Among these binding proteins, sialic acid residues were contained in 67BP, L-selectin, and NCA90, but not in the 28-kD and 49-kD proteins. Sialidase treatment completely abolished both the binding affinity of the type IV %collagen%-binding proteins to type IV %collagen% and the neutrophil adherence to type IV %collagen%-coated plastic. Thus, the sialic acid residues of 67BP, L-selectin, and NCA90 seem to be important for the binding of neutrophils to type IV %collagen%. Furthermore, L-selectin IgG %chimeric% protein directly bound to type IV %collagen%-Sepharose column, and anti-L-selectin MoAb DREG56 inhibited the neutrophil adherence to type IV %collagen%-coated plastic by 51%. These observations suggest that

L-selectin likely plays a role in the neutrophil binding to type IV  
%%collagen%%, although neutrophils have several kinds of adhesion  
molecules for type IV %%collagen%% such as L-selectin, NCA90, 67BP, and  
the 28-kD and 49-kD proteins.

7/7/19

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13159884 BIOSIS NO.: 199698627717

Isolation of endothelial-like stromal cells that express Kit ligand and  
support in vitro hematopoiesis

AUTHOR: Fleischman Roger A (Reprint); Simpson Frank; Gallardo Teresa; Jin  
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JOURNAL: Experimental Hematology (Charlottesville) 23 (13): p1407-1416  
1995 1995

ISSN: 0301-472X

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RECORD TYPE: Abstract

LANGUAGE: English

ABSTRACT: Although macrophages account for 70-90% of the adherent cells in  
mouse long-term bone marrow cultures (LTBMC) and CFU-F colonies, the  
predominant nonhematopoietic stromal cell is endothelial-like (EL),  
expressing cytoplasmic %%collagen%% IV, %%laminin%%, and an antigen  
recognized by the monoclonal antibody MECA-10. We report the isolation of  
this stromal cell lineage from primary LTBMC by immunomagnetic cell  
selection using MECA-10. More than 95% of the cells in the  
MECA-10-positive fraction are EL cells as judged by morphology, surface  
staining for MECA-10, cytoplasmic staining for %%collagen%% IV, and  
electrophoretic analysis of MECA-10-positive cells isolated from  
radiation %%chimeras%%. When plated under LTBMC conditions, EL cell  
monolayers recharged with either wild-type or Sl/Sl-d marrow support an  
increased density and number of clonogenic and mature hematopoietic cells  
in short-term cultures. In accord with this finding, Northern blots of  
mRNA from unstimulated EL cells demonstrate constitutive expression of  
Kit ligand (KL). Moreover, in situ two-color immunofluorescence staining  
for cytoplasmic %%collagen%% IV and surface KL suggests that EL cells  
are the exclusive source of membrane-bound KL in mouse cultures. The  
ability to isolate EL cells from primary cultures without the need for  
repeated cell passage or immortalization provides a novel approach to  
dissecting the molecular basis of stem cell-stromal cell interactions.

7/7/20

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12847730 BIOSIS NO.: 199598315563

Spreading and focal contact formation of human melanoma cells in response  
to the stimulation of both melanoma-associated proteoglycan (NG2) and  
alpha-4-beta-1 integrin

AUTHOR: Iida Joji (Reprint); Meijne Alexandra M L; Spiro Robert C; Roos Ed;  
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JOURNAL: Cancer Research 55 (10): p2177-2185 1995 1995  
ISSN: 0008-5472  
DOCUMENT TYPE: Article  
RECORD TYPE: Abstract  
LANGUAGE: English

ABSTRACT: In this study, we evaluated the potential role for a specific melanoma-associated chondroitin sulfate proteoglycan core protein, termed NG2, to collaborate with alpha-4-beta-1 integrin in focal contact formation in human melanoma cells. Although melanoma cells adhered to substrata coated with either the alpha-4-beta-1 integrin binding fibronectin synthetic peptide CS1OVA or anti-NG2 mAbs, no spreading or focal contact formation was observed on either substratum. However, melanoma cells spread and formed focal contacts on "%%chimeric%% substrata" coated with CS1-OVA and the anti-NG2 mAb, 9.2.27, indicating that engaging both adhesion receptors changes the adhesion phenotype of melanoma cells by reorganizing the cytoskeleton. The collaboration between the two receptors is specific to fibronectin, since cells adherent on substrata coated with low concentrations of either %%laminin%% and 9.2.27 or type IV %%collagen%% and 9.2.27 failed to spread, while cells adherent on low concentrations of fibronectin and 9.2.27 exhibited a fully spread morphology. Two selective tyrosine kinase inhibitors, genistein and herbimycin A, totally inhibited cell spreading on the substrata coated with CS1-OVA and 9.2.27, indicating that tyrosine kinase(s) is important for cell spreading and focal contact formation. When cells were cultured on substrata coated with CS1-OVA and 9.2.27, two proteins (M-r 130,000 and 120,000) were tyrosine phosphorylated in a genistein- and herbimycin A-sensitive fashion. These proteins were not immunologically related to pp125-FAK or alpha-4-beta-1 integrin. Importantly, when melanoma cells were cultured on substrata coated with CS1 and then stimulated with 9.2.27-conjugated microsphere beads, formation of focal contacts and stress fibers was also observed, indicating that NG2 can collaborate with alpha-4-beta-1 integrin when each receptor is engaged on distinct and separate substrata. These results demonstrate that NG2 acts as a coreceptor for spreading and focal contact formation in association with alpha-4-beta-1 integrin in melanoma cells and suggest a model in which the NG2 core protein communicates to alpha-4-beta-1 integrin by an inside-out signaling mechanism.

7/7/21

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12606735 BIOSIS NO.: 199598074568

The VLA-2 (alpha-2-beta-1) I domain functions as a ligand-specific recognition sequence for endothelial cell attachment and spreading: Molecular and functional characterization

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JOURNAL: Blood 84 (11): p3734-3741 1994 1994  
ISSN: 0006-4971  
DOCUMENT TYPE: Article  
RECORD TYPE: Abstract

LANGUAGE: English

ABSTRACT: The integrin VLA-2 (alpha-2-beta-1), generally considered to represent the specific **collagen** receptor on human endothelial cells, contains an alpha-2-subunit inserted I domain with structural similarity to the type A domains found within the recently described superfamily of receptor-ligand recognition proteins. This region of the cDNA has now been isolated and used for molecular and functional characterization of this heterodimeric receptor complex. Comparative sequence analysis with the porcine homologue revealed 93% amino acid sequence identity, suggestive of a developmentally conserved function. To complete structure/function studies, this region of the human cDNA was expressed as a **chimeric** protein in Escherichia coli, and a rabbit polyclonal antibody (anti-I domain) was used to study determinants of endothelial cell attachment and spreading in vitro. Quantifiable and visual disruption of endothelial cell attachment to gelatin, type I **collagen**, and **laminin** was evident using the specific anti-I domain antibody, with minimal inhibitory effects demonstrable using fibronectin or fibrinogen matrices. Therefore, these data would suggest that the alpha-2-beta-1 domain confers ligand-binding specificity for both known alpha-2-beta-1 substrates (**laminin** and **collagen**), and that this region subserves a regulatory function in the molecular processes controlling endothelial cell attachment and spreading in vitro.

7/7/22

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12474437 BIOSIS NO.: 199497495722

The role of the I domain in ligand binding of the human integrin  
alpha-1-beta-1

AUTHOR: Kern Andreas; Brieswitz Roger; Bank Ilan; Marcantonio Eugene E  
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JOURNAL: Journal of Biological Chemistry 269 (36): p22811-22816 1994 1994

ISSN: 0021-9258

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LANGUAGE: English

ABSTRACT: We report here the analysis of potential ligand binding domains within the human integrin alpha-1 subunit, a known **collagen**/**laminin** receptor. This integrin is effectively blocked by the mouse monoclonal antibody 1B3.1. A truncated version of the alpha-1 subunit lacking the NH-2-terminal half of the extracellular domain is not recognized by monoclonal antibody 1B3.1. Furthermore, we have isolated a cDNA containing the I domain from chicken alpha-1 bearing significant homology to the human and rat alpha-1 sequences. Replacing the human I domain with its chicken counterpart led to the surface expression of a functional heterodimer with endogenous mouse beta-1 on NIH 3T3 cells. However, 1B3.1 does not bind to the chicken/human **chimera**, demonstrating that the human alpha-1 I domain is required for epitope recognition. Mutation of Asp-253 within the I domain to alanine resulted in surface expression of an alpha-beta heterodimer recognized by 1B3.1 but with markedly reduced binding to **collagen** IV or **laminin**.

Since a previously reported mutation of a homologous Asp in the Mac-1 I domain has similar consequences, these results suggest a central role for the I domain in ligand recognition for all integrin alpha subunits containing this domain.

7/7/23

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12351090 BIOSIS NO.: 199497372375

Regulation of extracellular matrix proteins and integrin cell substratum adhesion receptors in epithelium during cutaneous human wound healing in vivo

AUTHOR: Juhasz Istvan; Murphy George F; Yan Horng-Chin; Herlyn Meenhard; Albelda Steven M (Reprint)

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JOURNAL: American Journal of Pathology 143 (5): p1458-1469 1993 1993

ISSN: 0002-9440

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RECORD TYPE: Abstract

LANGUAGE: English

ABSTRACT: Although changes in extracellular matrix proteins during wound healing have been well documented, little is known about the regulation of corresponding extracellular matrix adhesion receptors (integrins). To study this process in a human in vivo model, full thickness human skin grafts were transplanted onto severe combined immunodeficient mice and deep excisional wounds involving both the epidermal and dermal layers were then made. The changes in the expression of cell matrix proteins and epithelial integrins over time were analyzed with specific antibodies using immunohistochemistry. Wounding was associated with alterations in extracellular matrix proteins, namely, loss of %laminin% and type IV %collagen% in the region of the wound and expression of tenascin and fibronectin. Changes were also noted in the integrins on the migrating keratinocytes. There was marked upregulation of the  $\alpha$ , subunit and de novo expression of the fibronectin receptor ( $\alpha$ -5- $\beta$ -1) during the stage of active migration (days 1 to 3 after wounding). In the later stages of wound healing, after epithelial integrity had been established, redistribution of the  $\alpha$ -2,  $\alpha$ -3,  $\alpha$ -6, and  $\beta$ -4 %collagen%/ %laminin%-binding integrin subunits to suprabasal epidermal layers was noted. Thus, during cutaneous wound healing, keratinocytes up-regulate fibronectin/fibrinogen-binding integrins and redistribute %collagen%/ %laminin%-binding integrins. This study demonstrates that the human skin/severe combined immunodeficient %chimera% provides a useful model to study events during human wound repair.

7/7/24

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11918975 BIOSIS NO.: 199396083391

Localization of the disulfide bonds in the amino-2-terminal domain of the cellular receptor for human urokinase-type plasminogen activator: A

domain structure belonging to a novel superfamily of glycolipid-anchored membrane proteins

AUTHOR: Ploug Michael (Reprint); Kjalke Marianne; Ronne Ebbe; Weidle Ulrich ; Hoyer-Hansen Gunilla; Dano Keld

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JOURNAL: Journal of Biological Chemistry 268 (23): p17539-17546 1993

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RECORD TYPE: Abstract

LANGUAGE: English

ABSTRACT: The receptor for human urokinase-type plasminogen activator (uPAR) is synthesized as a 313-residue-long polypeptide containing 28 cysteine residues, the pattern of which defines three homologous repeats within the protein. These entities are believed to represent a novel protein domain structure, of which the NH-2terminal domain of uPAR can be covalently cross-linked to the epidermal growth factor-like module of urokinase after receptor-ligand interaction. The NH-2-terminal domain of a recombinant, soluble uPAR derivative, labeled with (35S)cysteine, was isolated after limited proteolysis with chymotrypsin. The four disulfide bonds present within this domain were assigned by a combination of plasma desorption mass spectrometry, amino acid composition, and sequence analyses of peptides generated by trypsin, endoprotease Asp-N, and thermolysin. The following disulfide bond structure was determined: Cys-3-Cys-24, Cys-6-Cys-12, Cys-17-Cys-45, and Cys-71-Cys-76. Similar cysteine pairing is likely to be found within other members of this protein superfamily, i.e., the membrane inhibitor of reactive lysis, Ly-6, and the remaining two domains of uPAR. However, an additional pair of cysteines present within these domains probably forms a fifth disulfide bond.

7/7/25

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11918974 BIOSIS NO.: 199396083390

Identification of a regulatory region of integrin beta-1 subunit using activating and inhibiting antibodies

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JOURNAL: Journal of Biological Chemistry 268 (23): p17597-17601 1993

ISSN: 0021-9258

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LANGUAGE: English

ABSTRACT: Members of the beta-1 integrin subfamily recognize multiple ligands such as fibronectin, laminin, and collagen and mediate cell-cell and cell-extracellular matrix interactions. beta-1 subunit may play a central role in regulating beta-1 integrin avidity. Here we have identified a small region of beta-1 subunit (residues 207-218) that is critical for the binding of both activating (8A2, A1A5, and TS2/16) and inhibiting (4B4, 4B5, 13, A1IB2, and P4C10) monoclonal antibodies against human beta-1 using interspecies chimeric beta-1

and site-directed mutagenesis. Chicken beta-1 that has human sequence within residues 207-218 (CH mutant) is recognized by all the human specific antibodies listed above. The region 207-218 is located between the two putative ligand binding sites (residues 120-182 and 220-231), and the amino acid sequence of the region involves a predicted bend structure. The other anti-beta-1 antibodies that do not affect cell attachment to ligands (K20, 102DF5, LM442, and LM534) recognized the carboxyl-terminal regions of extracellular domain of beta-1 (residues 426-587 for K20 and 588-708 for 102DF5, LM442, and LM534, respectively). Our data suggest a potential mechanism for the avidity regulation of beta-1 integrin through conformational changes of beta-1 subunit.

7/7/26

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11288877 BIOSIS NO.: 199293131768

DISTINCT CELLULAR FUNCTIONS MEDIATED BY DIFFERENT VLA INTEGRIN ALPHA  
SUBUNIT CYTOPLASMIC DOMAINS

AUTHOR: CHAN B M C (Reprint); KASSNER P D; SCHIRO J A; BYERS H R; KUPPER T  
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JOURNAL: Cell 68 (6): p1051-1060 1992

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ABSTRACT: To characterize VLA .alpha. subunit cytoplasmic domain functions, unaltered .alpha.2 cDNA (called X2C2) and two %%%chimeric%%% cDNAs (called X2C5 and X2C4) were constructed with extracellular .alpha.2 domains and cytoplasmic .alpha.2, .alpha.5, and .alpha.4 domains respectively. Upon transfection into rhabdomyosarcoma (RD) cells, each construct yielded comparable expression levels, immunoprecipitation profiles, and avidity for %%%collagen%%% and %%%laminin%%%. However, while RDX2C2 and RDX2C5 transfectants mediated %%%collagen%%% gel contraction, RDX2C4 and a mock transfectant (RDpF) did not. Conversely, only RDX2C4 cells (but not RDX2C2 or RDX2C5) showed enhanced cell migration on %%%collagen%%% and %%%laminin%%% compared with RDpF cells. This indicates markedly differing roles for integrin .alpha. subunit cytoplasmic domains in post-ligand binding events. Furthermore, stable exertion of physical force (%%%collagen%%% gel contraction) may involve fundamentally different cellular machinery than the transient adhesion occurring during cell migration. Finally, these findings provide insight into a functional flexibility perhaps resulting from multiple integrins binding to identical ligands.

7/7/27

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10161571 BIOSIS NO.: 199089079462

STROMAL CELL PROGENY OF MURINE BONE MARROW FIBROBLASTS COLONY-FORMING UNITS  
ARE CLONAL ENDOTHELIAL-LIKE CELLS THAT EXPRESS %%%COLLAGEN%%% IV AND

%%LAMININ%%

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JOURNAL: Blood 75 (3): p620-625 1990  
ISSN: 0006-4971  
DOCUMENT TYPE: Article  
RECORD TYPE: Abstract  
LANGUAGE: ENGLISH

ABSTRACT: Studies of human and murine bone marrow explants have demonstrated that existence of stromal cell precursors that give rise to colonies of adherent cells in short-term cultures. Because previous data suggested that these colonies were composed of fibroblasts, the precursor cells were termed fibroblast colony-forming units (CFU-F). However, we have recently shown that the stromal cells which support hematopoiesis in murine long-term bone marrow cultures (LTBC) express %%collagen%% IV and %%laminin%%, markers associated with an endothelial cell lineage, but are negative for %%collagen%% I and III, markers associated with a fibroblast cell lineage. Because these conflicting results suggest major functional differences between the stromal cells observed in long-term cultures and the short-term assay, we re-examined the lineage of CFU-F-derived stromal cells. Using two-color immunofluorescence, we characterized virtually all of the cells comprising individual "CFU-F" colonies derived from mouse radiation %%chimeras%%. Identification of donor (hematopoietic) or host (stromal) origin was based on surface staining for strain-specific H-2 surface antigens, and, for endothelial or fibroblast properties, on cytoplasmic staining for %%laminin%% and %%collagen%% IV, or collagens I and III, respectively. The results demonstrate that a large proportion of the cells in CFU-F colonies are donor-derived and fail to stain with any of the antisera specific for nonhematopoietic cells. In addition, these donor-derived cells exhibit marked phagocytic capacity and stain positively with monoclonal antibodies characteristic of the mono-macrophage hematopoietic cell lineage (anti-T200, anti-Mac-1, F4/80). However, the remainder of the cells are host-derived cells that stain positively with antisera to %%collagen%% IV and %%laminin%%. In contrast, stains for %%collagen%% types I and III were negative under conditions that allowed for strong staining of control skin fibroblasts. In separate studies, using mixtures of two genetically distinct bone marrows, the cells expressing %%collagen%% IV were further shown to be clonal in origin within individual colonies, directly demonstrating that the CFU-F assay provides a quantitative measure of the numbers of marrow stroma cell precursors. Thus, the current studies establish a remarkable similarity between the hematopoietic microenvironment in the short-term CFU-F assay and the long-term culture system: the majority of adherent cells are hematopoietic cells of the monocyte-macrophage lineage, while the remainder are stromal cells whose precise lineage remains uncertain, but whose pattern of %%collagen%% expression is more consistent with an endothelial rather than a fibroblast cell origin.

7/7/28

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09160939 BIOSIS NO.: 198886000860

HEMATOPOIETIC MICROENVIRONMENT ORIGIN LINEAGE AND TRANSPLANTABILITY OF THE  
STROMAL CELLS IN LONG-TERM BONE MARROW CULTURES FROM %%%CHIMERIC%%% MICE  
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JOURNAL: Journal of Clinical Investigation 81 (4): p1072-1080 1988  
ISSN: 0021-9738  
DOCUMENT TYPE: Article  
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LANGUAGE: ENGLISH

ABSTRACT: Studies of bone marrow transplant patients have suggested that the stromal cells of the in vitro hematopoietic microenvironment are transplantable into conditioned recipients. Moreover, in patients with myeloproliferative disorders, all of the stromal cells, which include presumptive endothelial cells, appear to be derived from hematopoietic precursors. To confirm these findings, we have constructed two %%%chimeric%%% mouse models: (a) traditional radiation %%%chimeras%%%, and (b) fetal %%%chimeras%%%, produced by placental injection of bone marrow into genetically anemic Wx/Wu fetuses, a technique that essentially precludes engraftment of nonhematopoietic cells. Using two-color indirect immunofluorescence, the stromal cells in long-term bone marrow culture derived from these %%%chimeras%%% were analyzed for donor or host origin by strain-specific H-2 antigens, and for cell lineage by a variety of other specific markers. 75-95% of the stromal cells were shown to be hematopoietic cells of the monocyte-macrophage lineage, based upon donor origin, phagocytosis, and expression of specific hematopoietic surface antigens. The remaining 5-25% of the stromal cells were exclusively host in origin. Apart from occasional fat cells, these cells uniformly expressed %%%collagen%%% type IV, %%%laminin%%%, and a surface antigen associated with endothelial cells. Since these endothelial-like cells are not transplantable into radiation or fetal %%%chimeras%%%, they are not derived from hematopoietic stem cells. The contrast between our findings and human studies suggest either unexpected species differences in the origin of stromal lineages or limitations in the previous methodology used to detect nonhematopoietic stromal cells.

7/7/29

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08277913 BIOSIS NO.: 198732006804  
AUTORADIOGRAPHIC STUDY OF THE ORIGIN OF BASEMENT MEMBRANE COMPONENTS IN THE AVIAN EMBRYO  
BOOK TITLE: SLAVKIN, H. C. (ED.). PROGRESS IN CLINICAL AND BIOLOGICAL RESEARCH, VOL. 217B. PROGRESS IN DEVELOPMENTAL BIOLOGY, PART B; TENTH INTERNATIONAL CONGRESS OF THE INTERNATIONAL SOCIETY OF DEVELOPMENTAL BIOLOGISTS, LOS ANGELES, CALIF., USA, AUG. 4-9, 1985. XXVIII+462P. ALAN R. LISS, INC.: NEW YORK, N.Y., USA. ILLUS  
AUTHOR: HARRISSON F (Reprint)  
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SERIES TITLE: Progress in Clinical and Biological Research p377-380 1986  
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0019597075 BIOSIS NO.: 200700256816

Injury to the thymic niche for DN2/DN3 developing T cells impairs  
reconstitution.

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JOURNAL: Blood 108 (11, Part 1): p24A-25A NOV 16 2006 2006

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RECORD TYPE: Abstract

LANGUAGE: English

ABSTRACT: Despite recovery of most hematopoietic functions, prolonged defects in generating functional T lymphocytes is a common occurrence after T cell depleted bone marrow transplant. While the mechanisms of these defects have not all been elucidated, contributing factors include age, T cell depletion of the graft, therapy with radiation and cytotoxic agents, and graft versus host disease (GvHD). We have designed an in vivo functional assessment of the ability of thymic stroma to support de novo T lymphocyte development. Mice deficient for the  $\alpha$  chain of the IL-7 receptor (IL7R  $\alpha$ -/-) support robust thymic reconstitution after transplant of limited numbers of congenic precursors. We demonstrated that this capacity for reconstitution of immunodeficient strains depends on the paucity of specific endogenous precursors (DN3) cells in the IL7R  $\alpha$ -/- thymus and reflects the presence of functionally normal but empty stromal niches in this immunodeficient strain. We have proceeded to demonstrate that a variety of chemotherapeutic agents as well as aging, impair the ability of IL7R  $\alpha$ -/- thymic stroma to support de novo T cell development. Some agents allow donor chimerism in the thymus, but not rescue of the hypocellularity (eg cyclophosphamide) while others do not affect reconstitution (eg fludarabine). Multi-agent regimens have been administered and in some instances demonstrate an additive detrimental impact on thymic reconstitution. For several agents, damage has been localized to specific stromal niches by isolating changes in lymphoid subsets and stromal keratin expression. Decreased availability of the stromal niche for DN3 progenitors is associated with a decreased frequency of DN3s and an absolute block in recipient IL7R  $\alpha$ -/- T cell development. In addition, RNA from treated and untreated thymic stromal cells has been used to evaluate the gene expression pattern in thymic stroma of IL7R  $\alpha$ -/- mice treated with cytotoxic agents. In one example to be presented we find decreased thymic reconstitution in mice



treated with Busulfan with sustained changes in stromal elements. These findings are consistent with sustained damage to thymic stromal cells. Among other changes, busulfan leads to decreased expression of % laminin % 5 by cortical thymic epithelial cells. The integrin heterodimer alpha 6 beta 4 is a binding partner for % laminin % 5 and is expressed uniformly by DN2 thymocytes. The significance of % laminin % 5/alpha 6 beta 4 signaling during T cell development was assessed using mice with a targeted mutation in the integrin beta 4 signaling domain. In these experiments mutant fetal liver was used to create hematopoietic % chimeras % and evaluate T cell development. Our studies provide insight into the nature of damage to thymic stroma by cytotoxic regimens and an understanding of the effect of this damage on subsequent immune reconstitution.

8/7/2

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18499611 BIOSIS NO.: 200510194111

Bifunctional peptides derived from homologous loop regions in the % laminin % % alpha % % chain % LG4 modules interact with both alpha 2 beta 1 integrin and syndecan-2

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JOURNAL: Biochemistry 44 (28): p9581-9589 JUL 19 2005 2005

ISSN: 0006-2960

DOCUMENT TYPE: Article

RECORD TYPE: Abstract

LANGUAGE: English

ABSTRACT: % Laminin % alpha chains show diverse biological functions in a chain-specific fashion. The % laminin % G-like modules (LG modules) of the % laminin % alpha chains consist of a 14-stranded beta-sheet sandwich structure with biologically active sequences found in the connecting loops. Previously, we reported that connecting loop regions between beta-strands E and F in the mouse % laminin % % alpha % % chain % LG4 modules exhibited chain-specific activities. In this study, we focus on the homologous loop regions in human % laminin % % alpha % % chain % LG4 modules using five synthetic peptides (hEF-1-hEF-5). These homologous peptides induced chain-specific cellular responses in various cell types. Next, to examine the dual-receptor recognition model, we synthesized % chimeras % (cEF13A-cEF13E) derived from peptides hEF-1 and hEF-3. All of the % chimeric % peptides promoted fibroblast attachment as well as the parental peptides. Attachment of fibroblasts to cEF13A and cEF13B was inhibited by anti-integrin alpha 2 and beta 1 antibodies and by heparin, while cell adhesion to cEF13C, cEF13D, and cEF13E was blocked only by heparin. Actin organization of fibroblasts on cEF13C was not different from that on hEF-3, but cEF13B induced membrane ruffling at the tips of the actin stress fibers. These results suggest that cEF13B had bifunctional effects on cellular behaviors through alpha 2 beta 1 integrin and heparin/heparan sulfate proteoglycan. We conclude that the approach utilizing

%%chimeric%% peptides is useful for examining cellular mechanisms in dual-receptor systems.

8/7/3

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14233868 BIOSIS NO.: 199800028115

The %%laminin%% alpha2-chain short arm mediates cell adhesion through both the alpha1beta1 and alpha2beta1 integrins

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JOURNAL: Journal of Biological Chemistry 272 (46): p29330-29336 Nov. 14, 1997 1997

MEDIUM: print

ISSN: 0021-9258

DOCUMENT TYPE: Article

RECORD TYPE: Abstract

LANGUAGE: English

ABSTRACT: %%Laminin%%-2, a heterotrimer composed of alpha2, beta1, and gamma1 subunits, is the primary %%laminin%% isoform found in muscle and peripheral nerve and is essential for the development and stability of basement membranes in these tissues. Expression of a domain VI-truncated %%laminin%% alpha2-chain results in muscle degeneration and peripheral nerve dysmyelination in the dy2J dystrophic mouse. We have expressed amino-terminal domains VI through IVb of the %%laminin%% alpha2-chain, as well as its %%laminin%%-1 alpha1-chain counterpart, to identify candidate cell-interactive functions of this critical region. Using integrin-specific antibodies, recognition sites for the alpha1/beta1 and alpha2beta1 integrins were identified in the short arms of both %%laminin%% alpha1- and alpha2-chain isoforms. Comparisons with a beta-alpha %%chimeric%% short arm protein possessing %%alpha%%-%%chain%% domain VI further localized these activities to %%alpha%%-%%chain%% domain VI. In addition, we found that the %%laminin%% alpha2-chain short arm supported neurite outgrowth independent of other %%laminin%%-2 subunits. A heparin/heparan sulfate binding activity was also localized to this region of the %%laminin%% alpha2 subunit. These data provide the first evidence that domain VI of the %%laminin%% alpha2-chain mediates interactions with cell surface receptors and suggest that these integrin and heparin binding sites, alone or in concert, may play an important role in muscle and peripheral nerve function.

? t s12/7/1

12/7/1

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07360509 BIOSIS NO.: 198478095916

ROLE OF PLEURAL MESOTHELIAL CELLS IN THE PRODUCTION OF THE SUBMESOTHELIAL

CONNECTIVE TISSUE MATRIX OF LUNG

AUTHOR: RENNARD S I (Reprint); JAURAND M-C; BIGNON J; KAWANAMI O; FERRANS V J; DAVIDSON J; CRYSTAL R G

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JOURNAL: American Review of Respiratory Disease 130 (2): p267-274 1984  
ISSN: 0003-0805

DOCUMENT TYPE: Article

RECORD TYPE: Abstract

LANGUAGE: ENGLISH

ABSTRACT: The pleura is comprised of a single layer of mesothelial cells resting on a complex layer of connective tissue. The ability of mesothelial cells to produce the components of this connective tissue was investigated using cultured rat mesothelial cells. These cells produced several components of extracellular matrix, including  $6.8 \pm 0.2$  times  $10^5$  %collagen% %pro%-.%alpha%-%chains% per cell per h, which represented  $3.09 \pm 0.05\%$  of all proteins synthesized by these cells. Chemical and immunologic criteria were used to demonstrate that these %collagen% chains included those of %collagen% types I, III and IV. These cells produced elastin, as well as the connective tissue glycoproteins %laminin% and fibronectin. EM studies revealed that lung mesothelial cells were capable of organizing these components into complex structures that resembled components of the extracellular matrix (thick %collagen% fibers, the amorphous component of elastic fibers and basement membranelike structures), and restricted the formation of these structures to the basal region below the cells in culture. Pleural mesothelial cells are active sources of a variety of connective tissue macromolecules found beneath mesothelial cells in situ, and can assemble these components into structures resembling the pleural extracellular matrix.

? t s13/7/1-13

13/7/1

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18912910 BIOSIS NO.: 200600258305

E-cadherin loss promotes the initiation of squamous cell carcinoma invasion through modulation of integrin-mediated adhesion

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JOURNAL: Journal of Cell Science 119 (2): p283-291 JAN 15 2006 2006

ISSN: 0021-9533

DOCUMENT TYPE: Article

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LANGUAGE: English

ABSTRACT: Much remains to be learned about how cell-cell and cell-matrix

interactions are coordinated to influence the earliest development of neoplasia. We used novel 3D human tissue reconstructs that mimic premalignant disease in normal epidermis, to directly investigate how loss of E-cadherin function directs conversion to malignant disease. We used a genetically tagged variant of Ha-Ras-transformed human keratinocytes (II-4) expressing dominant-interfering E-cadherin fusion protein (H-2k(d)-Ecad). These cells were admixed with normal human keratinocytes and tumor cell fate was monitored in 3D reconstructed epidermis upon transplantation to immunodeficient mice. Tumor initiation was suppressed in tissues harboring control- and mock-infected II-4 cells that lost contact with the stromal interface. By contrast, H-2k(d)-Ecad-expressing cells persisted at this interface, thus enabling incipient tumor cell invasion upon in vivo transplantation. Loss of intercellular adhesion was linked to elevated cell surface expression of alpha 2, alpha 3 and beta 1 integrins and increased adhesion to laminin-1 and Types I and IV collagen that was blocked with beta 1-integrin antibodies, suggesting that invasion was linked to initial II-4 cell attachment at the stromal interface. Collectively, these results outline a novel aspect to loss of E-cadherin function that is linked to the mutually interdependent regulation of cell-cell and cell-matrix adhesion and has significant consequences for the conversion of premalignancy to cancer.

13/7/2

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18583807 BIOSIS NO.: 200510278307

Endostatin phenylalanines 31 and 34 define a receptor binding site

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JOURNAL: Genes to Cells 10 (9): p929-939 SEP 2005 2005

ISSN: 1356-9597

DOCUMENT TYPE: Article

RECORD TYPE: Abstract

LANGUAGE: English

ABSTRACT: Endostatin has achieved much attention as a naturally occurring inhibitor of angiogenesis and tumor growth. Endostatin is derived from collagen XVIII's C-terminal domain and deleted or truncated in most patients suffering from Knobloch syndrome blindness. To evaluate the functional significance of two surface-exposed hydrophobic phenylalanines at positions 31 and 34 of endostatin and two human sequence alterations within endostatin, A48T and D104N, we applied the alkaline phosphatase fusion protein method. Replacement of F31 and F34 with alanines led to complete loss of characteristic in situ binding while heparin binding remained intact. In contrast, a non-heparin binding alkaline phosphatase-tagged human endostatin lacking R27 and R139 bound to specific tissue structures. The two Knobloch syndrome-associated endostatin sequence variants did not result in altered in situ binding to murine embryonal tissues, human endothelial cells, heparin and immobilized laminin. However, expression of the endostatin mutant A48T was significantly reduced. This observation may be explained by a

lower folding efficiency due to the structural constraints of A48 residing in the hydrophobic core. Our data suggest that residues F31 and F34 form a putative receptor binding site acting independently from heparan sulfate binding and that the A48T mutation destabilizes the endostatin molecule.

13/7/3

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17557343 BIOSIS NO.: 200300512706

ANNEXIN 2 IS REQUIRED FOR PHAGOCYTOSIS OF ROD OUTER SEGMENTS BY RETINAL PIGMENT EPITHELIAL CELLS

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JOURNAL: ARVO Annual Meeting Abstract Search and Program Planner 2003 p Abstract No. 1532 2003 2003

MEDIUM: cd-rom

CONFERENCE/MEETING: Annual Meeting of the Association for Research in Vision and Ophthalmology Fort Lauderdale, FL, USA May 04-08, 2003; 20030504

SPONSOR: Association for Research in Vision and Ophthalmology

DOCUMENT TYPE: Meeting; Meeting Poster; Meeting Abstract

RECORD TYPE: Abstract

LANGUAGE: English

ABSTRACT: Purpose The aim of this study was to examine whether retinal pigment epithelial cell annexin 2 has a role in phagocytosis of rod photoreceptor outer segments (ROS). Methods We have used ARPE19 cells (a human retinal pigmented epithelial cell line) grown on lens capsule or tissue culture plates coated with extracellular matrix proteins to model the RPE monolayer in association with Bruch's membrane. RPE cells expressing an annexin 2-green fluorescent protein fusion construct were cultured in the presence of Alexa red-labelled ROS, and imaged by confocal microscopy. ROS internalisation was quantified by analysis of digitized images, and comparisons were made between cells grown on different substrates in the presence or absence of small interfering RNAs against annexin 2. Results ARPE19 cells grown on polypropylene, fibronectin or vitronectin were poorly phagocytic but when the cells were grown on lens capsule, %laminin% or %collagen% IV their ability to phagocytose ROS improved significantly. The increase in phagocytic competence was paralleled by an increase in annexin 2 expression. siRNA-mediated depletion of annexin 2 in cells grown on these substrates attenuated the increase in phagocytic function, as did expression of a dominant negative mutant of annexin 2 in RPE cells grown on lens capsule. Using confocal microscopy we also observed enrichment of annexin 2 to the phagocytic cup during the preliminary stages of ROS adhesion, filopod extension and cup invagination. Conclusion We have shown that high levels of phagocytic competence in RPE cells correlate with high levels of annexin 2 expression. Interfering with annexin 2 function leads to significantly impaired phagocytic function, indicating an essential role for annexin 2 in this process.

13/7/4

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16475385 BIOSIS NO.: 200200068896

Interaction of the leucine-rich repeats of polycystin-1 with extracellular matrix proteins: Possible role in cell proliferation

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JOURNAL: Journal of the American Society of Nephrology 13 (1): p19-26  
January, 2002 2002

MEDIUM: print

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RECORD TYPE: Abstract

LANGUAGE: English

ABSTRACT: Polycystin-1, the product of the PKD1 gene, is a membrane-bound multidomain protein with a unique structure and a molecular weight of approx 460 kD. The purpose of this study is to investigate the binding of the cysteine-flanked leucine-rich repeats (LRR) of polycystin-1 to extracellular matrix (ECM) components. These interactions may play a role in normal renal development as well as the pathogenesis of autosomal-dominant polycystic kidney disease (ADPKD). In vitro assays were used to assess the binding of a fusion protein containing the LRR of polycystin-1 and that of affinity purified polycystin-1 to a number of ECM components. The results showed that the LRR modulate the binding of polycystin-1 to collagen I, fibronectin, laminin, and cyst fluid-derived laminin fragments. The addition of the LRR fusion protein to cells in culture resulted in a significant dose-dependent reduction in the rate of proliferation. Cyst fluid-derived laminin fragments had a stimulatory effect on cell proliferation, which was reversed by the LRR fusion protein. These results suggest that the LRR of polycystin-1 act as mediators of the polycystin-1 interaction with the ECM. The observed suppression effect of the LRR on cell proliferation suggests a functional role of the LRR-mediated polycystin-1 involvement in cell-matrix and cell-cell interactions. These interactions may result in the enhanced cell proliferation that is a characteristic feature of ADPKD.

13/7/5

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16197689 BIOSIS NO.: 200100369528

Connections between HP1H5alpha-mediated gene silencing and breast cancer metastatic phenotype in human and Drosophila models

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JOURNAL: Proceedings of the American Association for Cancer Research Annual Meeting 42 p60 March, 2001 2001

MEDIUM: print

CONFERENCE/MEETING: 92nd Annual Meeting of the American Association for  
Cancer Research New Orleans, LA, USA March 24-28, 2001; 20010324  
SPONSOR: American Association for Cancer Research  
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13/7/6

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15830974 BIOSIS NO.: 200100002813

Integrin alphasbeta1 and transforming growth factor-beta1 play distinct  
roles in Alport glomerular pathogenesis and serve as dual targets for  
metabolic therapy

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JOURNAL: American Journal of Pathology 157 (5): p1649-1659 November, 2000  
2000

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RECORD TYPE: Abstract

LANGUAGE: English

ABSTRACT: Alport syndrome is a genetic disorder resulting from mutations in  
type IV collagen genes. The defect results in pathological changes  
in kidney glomerular and inner-ear basement membranes. In the kidney,  
progressive glomerulonephritis culminates in tubulointerstitial fibrosis  
and death. Using gene knockout-mouse models, we demonstrate that two  
different pathways, one mediated by transforming growth factor  
(TGF)-beta1 and the other by integrin alphasbeta1, affect Alport  
glomerular pathogenesis in distinct ways. In Alport mice that are also  
null for integrin alpha1 expression, expansion of the mesangial matrix  
and podocyte foot process effacement are attenuated. The novel  
observation of nonnative laminin isoforms (laminin-2 and/or  
laminin-4) accumulating in the glomerular basement membrane of  
Alport mice is markedly reduced in the double knockouts. The second  
pathway, mediated by TGF-beta1, was blocked using a soluble fusion  
protein comprising the extracellular domain of the TGF-beta1 type  
II receptor. This inhibitor prevents focal thickening of the glomerular  
basement membrane, but does not prevent effacement of the podocyte foot  
processes. If both integrin alphasbeta1 and TGF-beta1 pathways are  
functionally inhibited, glomerular foot process and glomerular basement  
membrane morphology are primarily restored and renal function is markedly  
improved. These data suggest that integrin alphasbeta1 and TGF-beta1 may  
provide useful targets for a dual therapy aimed at slowing disease  
progression in Alport glomerulonephritis.

13/7/7

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14913026 BIOSIS NO.: 199900172686

Two-hybrid analysis reveals multiple direct interactions for thrombospondin

1

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JOURNAL: Matrix Biology 17 (6): p401-412 Oct., 1998 1998

MEDIUM: print

ISSN: 0945-053X

DOCUMENT TYPE: Article

RECORD TYPE: Abstract

LANGUAGE: English

ABSTRACT: The yeast two-hybrid system was used to reveal the interactions between proteins residing within the cutaneous basement membrane zone and other gene products expressed in cultured human keratinocytes. The proteins of interest included type VII %%%collagen%%%, the predominant component of anchoring fibrils, and %%%laminin%%% 5, a component of anchoring filaments. Although the two-hybrid system was not able to verify a direct interaction between the type VII %%%collagen%%% NC1 domain and the short arm of Lambeta3, the type VII %%%collagen%%% NC1 domain (tVII/NC1) and the %%%laminin%%% 5 beta3 chain globular domain VI (lam5/beta3) cDNAs; when used as baits, detected four overlapping cDNA clones encoding thrombospondin 1 (TSP1). The overlapping region of these cDNAs encodes amino acids 400-459, a segment included within a 70 kDa chymotryptic fragment known to bind type V %%%collagen%%%, %%%laminin%%% -1 and other matrix components. The type VII %%%collagen%%% NC1/TSP1 interaction was confirmed by exchanging the vectors, and the interacting domain was mapped by testing a set of both 5' and 3' deletion constructs. The central region of TSP1, when used as a bait in two-hybrid system, showed strong binding to the fibronectin (FN) type III-like repeats 4-7 of type VII %%%collagen%%% NC1 domain. The TSP1 bait also interacted with %%%laminin%%% 5 beta3 chain domain V/III, and the TSP1/%%%laminin%%% 5 beta3 chain interaction was verified by a GST-%%%fusion%%% %%%protein%%% interaction assay. The transcripts encoding TSP1, TSP2, Lambeta3 and type VII %%%collagen%%% were abundant in cultured foreskin keratinocytes, and the expression of TSP1 and TSP2 in a wide variety of adult and fetal tissues was confirmed by PCR analysis of multiple tissue cDNA panels. Furthermore, TSP1 type I repeats showed self interaction, and recognized a clone for extracellular matrix protein fibrillin-2. In addition, clones encoding angiogenesis related protein Jagged1 and a platelet enzyme phospholipase scramblase were identified. Thus, the results indicate several previously undetected interactions of TSP1, which is known to be highly expressed during embryonic development, tissue remodeling and wound healing.

13/7/8

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13682717 BIOSIS NO.: 199799316777

Macrophage metalloelastase degrades matrix and myelin proteins and

processes a tumour necrosis factor-alpha %%%fusion%%% %%%protein%%%

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JOURNAL: Biochemical and Biophysical Research Communications 228 (2): p  
421-429 1996 1996  
ISSN: 0006-291X  
DOCUMENT TYPE: Article  
RECORD TYPE: Abstract  
LANGUAGE: English

ABSTRACT: The matrix metalloproteinases (MMPs) are a group of enzymes which have the ability to degrade extracellular matrix. They also cleave non-matrix proteins such as myelin basic protein and alpha-1-antitrypsin and they are able to process tumour necrosis factor-alpha (TNF) to its mature form. We have cloned, expressed and purified human macrophage metalloelastase (EC 3.4.24.65), an MMP recognised for its ability to degrade elastin, but whose substrate specificity has not yet been defined. With the exception of type I ~~collagen~~ this enzyme degraded all matrix proteins tested, namely: type IV ~~collagen~~, type I gelatin, fibronectin, ~~laminin~~, vitronectin and proteoglycan. It also degraded myelin basic protein, cleaved alpha-1-antitrypsin and released TNF from a pro-TNF ~~fusion~~ ~~protein~~. Thus, in common with several other MMPs, macrophage metalloelastase has a broad substrate range which extends beyond that of elastin alone.

13/7/9

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13501666 BIOSIS NO.: 199699135726

A functional monoclonal antibody recognizing the human alpha-1-integrin I-domain

AUTHOR: Fabbri M; Castellani P; Gotwals P J; Kotelianski V; Zardi L; Zocchi M R

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JOURNAL: Tissue Antigens 48 (1): p47-51 1996 1996

ISSN: 0001-2815

DOCUMENT TYPE: Article

RECORD TYPE: Abstract

LANGUAGE: English

ABSTRACT: alpha-1-beta-1 heterodimer is a member of the integrin receptor superfamily that has been described to be involved in cell-matrix binding through its interaction with collagens, fibronectin and ~~laminin~~. The alpha-1 integrin belongs to a subset of I-domain containing integrins that includes alpha-M, alpha-L, alpha-X and alpha-2. In this study we describe an anti-alpha-1 mAb (FB 12) that recognizes an epitope located in the human alpha-1 I-domain, since the mAb can bind to human, but not to rat, recombinant I-domain GST ~~fusion~~ ~~protein~~. FB12 mAb efficiently and specifically inhibits the binding of activated human lymphocytes to ~~laminin~~, ~~collagen~~ and fibronectin. These data support the notion that the alpha-1 I-domain itself has an important role in receptor-ligand binding. In particular, we show that alpha-1 integrin-dependent lymphocyte adhesion to fibronectin is I-domain mediated, at variance with the RGD-dependent adhesion which seems to be mediated by the beta-1 rather than the alpha-1 integrin chain. Lastly,

the overexpression of the alpha-1-integrin by stromal cells and blood vessels of solid tumors may suggest a role for this integrin in tumor biology.

13/7/10

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12869285 BIOSIS NO.: 199598337118

Production and Properties of a Bifunctional %Fusion% %Protein% that Mediates Attachment of Vero Cells to Cellulosic Matrices

AUTHOR: Wierzba Andrew; Reichl Ado; Turner Robin F B; Warren R Antony J; Kilburn Douglas G (Reprint)

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JOURNAL: Biotechnology and Bioengineering 47 (2): p147-154 1995 1995

ISSN: 0006-3592

DOCUMENT TYPE: Article

RECORD TYPE: Abstract

LANGUAGE: English

ABSTRACT: The sequence Arg-Gly-Asp (RGD) in extracellular matrix proteins such as fibronectin, %collagen%, and %laminin% mediates cell attachment by interacting with proteins of the integrin family of cell surface receptors. A gene fusion encoding the RGD-containing peptide, fused to the C-terminus of a cellulose-binding domain (CBD/RGD), was expressed in Escherichia coli. Cultures produced up to 50 mg of CBD/RGD per liter, most of which was extracellular. It was purified from the culture supernatant by affinity chromatography on cellulose. CBD/RGD promoted the attachment of green monkey Vero cells to polystyrene and cellulose acetate. Attachment was inhibited by small synthetic peptides containing the RGD sequence. CBD/RGD was as effective as %collagen% in promoting the attachment of Vero cells to Cellsnow microcarriers.

13/7/11

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12849206 BIOSIS NO.: 199598317039

Beta-8 integrins mediate interactions of chick sensory neurons with %laminin%-1, %collagen% IV, and fibronectin

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JOURNAL: Molecular Biology of the Cell 6 (4): p419-431 1995 1995

ISSN: 1059-1524

DOCUMENT TYPE: Article

RECORD TYPE: Abstract

LANGUAGE: English

ABSTRACT: Integrins are major receptors used by cells to interact with extracellular matrices. In this paper, we identify the first ligands for the beta-8 family of integrins, presenting evidence that integrin heterodimers containing the beta-8 subunit mediate interactions of chick sensory neurons with %laminin%-1, %collagen% IV, and fibronectin.

A polyclonal antibody, anti-beta-8-Ex, was prepared to a bacterial %fusion% protein% expressing an extracellular portion of the chicken beta-8 subunit. In nonreducing conditions, this antibody immunoprecipitated from surface-labeled embryonic dorsal root ganglia neurons a M-r 100 k protein, the expected M-r of the beta-8 subunit, and putative alpha subunit(s) of M-r 120 k. Affinity-purified anti-beta-8-Ex strongly inhibited sensory neurite outgrowth on %laminin%-1, %collagen% IV, and fibronectin-coated substrata. Binding sites were identified in a heat-resistant domain in %laminin%-1 and in the carboxyl terminal, 40-kDa fibronectin fragment. On substrates coated with the carboxyl terminal fragment of fibronectin, antibodies to beta-1 and beta-8 were only partially effective alone, but were completely effective in combination, at inhibiting neurite outgrowth. Results thus indicate that the integrin beta-8 subunit in association with one or more alpha subunits forms an important set of extracellular matrix receptors on sensory neurons.

13/7/12

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T-cell activation molecule 4-1BB binds to extracellular matrix proteins

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ABSTRACT: The recently isolated 4-1BB cDNA clone encodes a cell surface protein expressed by activated T cells. Its extracellular domain is homologous to members of the nerve growth factor receptor super family and its cytoplasmic domain contains a sequence homologous to the binding site for the T-cell-specific tyrosine kinase p56-lck found in the cytoplasmic domains of CD4 and CD8-alpha. At present the function of 4-1BB is not known. We prepared a 4-1BB-immunoglobulin %fusion% protein% (4-1BB Rg). This protein was used in immunohistochemical studies to identify tissues that express the 4-1BB ligand. 4-1BB Rg bound to virtually all tissues examined, suggesting that extracellular components might function as its ligands. To explore this possibility, 4-1BB was expressed in COS cells and found to mediate the binding of fibronectin, vitronectin, %laminin%, and %collagen% VI but not of %collagen% I. The binding of extracellular matrix proteins to 4-1BB was not mediated by Arg-Gly-Asp (RGD) or CS-1 amino acid sequences. Experiments with overlapping proteolytic fragments of fibronectin showed that 4-1BB interacts with multiple regions of fibronectin. The interaction between extracellular matrix proteins and 4-1BB was completely blocked by the anionic carbohydrate polymer fucoidan and was partially blocked by the anionic carbohydrate polymer dextran sulfate and the glycosaminoglycan heparin sulfate but was unaffected by desulfated heparin. These results suggest that carbohydrates may play a role in

mediating the 4-1BB-extracellular matrix protein adhesion.

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RETINOIC ACID RECEPTOR EXPRESSION VECTOR INHIBITS DIFFERENTIATION OF F9  
EMBRYONAL CARCINOMA CELLS

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ABSTRACT: Expression vectors have been constructed for a region of the human retinoic acid receptor-alpha (hRAR-alpha) and transferred into F9 embryonal carcinoma (EC) cells. When the vectors are overexpressed in F9 cells, clones can be selected for resistance to retinoic acid-induced differentiation. This effect is obtained even when the hRAR-alpha region is expressed as a .beta.-galactosidase %%%fusion%%% %%%protein%%%. Using the .beta.-galactosidase component of the %%%fusion%%% %%%protein%%% as a marker, overexpression of the %%%fusion%%% %%%protein%%% has been correlated with the retinoic acid-resistance effect. The clones resistant to retinoic acid no longer exhibit the normal retinoic acid induction of endo B cytokeratin, %%%laminin%%% B-1, and tissue plasminogen activator mRNAs observed with normal F9 cells. Retinoic acid induction of type IV alpha-1 %%%collagen%%% and Hox-1.3 RNAs is observed with these clones. When transfected with a thyroid receptor DNA-binding sequence (TRE)/thymidine kinase promoter/luciferase construct, the retinoic acid-resistant clones do not yield the same retinoic acid-induced level of luciferase obtained with F9 cells. It is hypothesized that the RAR vectors are interfering with endogenous RAR (s) in a dominant-negative manner to inhibit retinoic acid-induced differentiation of F9 EC cells.

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